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PROFOUND HYPOTHERMIA WITH SIMPLIFIED EQUIPMENT: A DISPOSABLE STAINLESS STEEL HEAT EXCHANGER OF HIGH EFFICIENCY

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SINCE the introduction of a blood heat exchanger into an extracorporeal perfusion apparatus by Gollan,[1] Delorme,[2] and Pierce[3] and the demonstration of the safety of experimental and clinical hypothermia for open-heart surgery and circulatory arrest by a number of workers,[4-11] blood heat exchangers have rapidly evolved into a number of designs (Fig. 1).

Commercially available blood heat exchangers, based on designs *C*, *D*, *E*, and *F* in Fig. 1, are cumbersome, expensive, difficult to clean, and contain internal seals which, if a leak occurs, may allow water to pass directly into the flowing stream of blood. In addition, the priming volume required is excessive even in the most efficient model of the group. We became interested in the problem of developing an efficient blood heat exchanger in mid 1959. From a consideration of the elements of heat transfer it was apparent that heat transfer is dependent upon (a) the area of surface developed between the

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blood and the cooling water. (b) It is dependent on the specific conductivity of the material used, expressed as calories transferred per square centimeter per minute for a unit thickness of 1 cm. for a temperature difference of 1° C. It was apparent, therefore, that heat transfer would be greatly improved

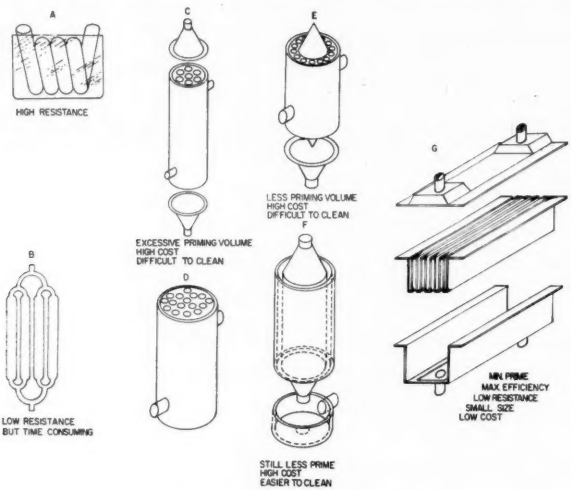

Fig. 1.—Schematic diagram illustrating the evolution of blood heat exchanger design.

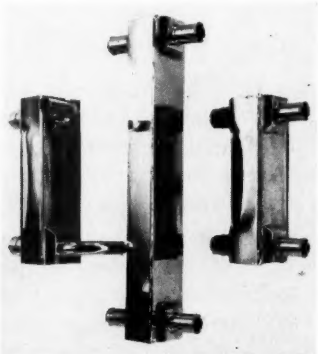

Fig. 2.—Two sizes of disposable stainless steel heat exchangers. Unit, five inches long, weighs 8 ounces and requires 60 c.c. of blood to prime. Unit, ten inches long, requires 95 c.c. of blood to prime. Various sizes and shapes of tube fittings can be employed for maximum utility.

if thin metal could be successfully employed. (c) The temperature difference between the fluids on the two sides of the exchanger should be maximized by maintaining the highest rate of flow possible in these fluids.

From a consideration of these principles, a design was evolved[14] (Fig. 1, *G*) which consists of a stainless steel sheet, five thousandths inch thick and 5 by 26½ inches in size, folded into a grid-like structure. The ends are

closed by two interdigitating combs of stainless steel, and the unit is enclosed in a stainless steel box having suitable manifolds for blood and cooling or warming water. The unit is fastened with a nontoxic solder composed of 95 per cent tin and 5 per cent silver. The interior is coated with Dow Corning No. 803 silicon resin. Since the unit is low in cost and cannot be perfectly recleaned for human surgery, it must be considered a one-use disposable item. Two sizes are being produced (Fig. 2), one 5 inches in length has a priming volume of 60 c.c. of blood and an area of 110 square inches and is equal in heat exchange ability to one standard Harrison-Brown exchanger. The second size which is 10 inches in length requires 95 c.c. of blood to prime, has an area of 220 square inches, and is equal in heat exchange ability to two Harrison-Brown units. A standard heat exchanger test on a 5 inch exchanger

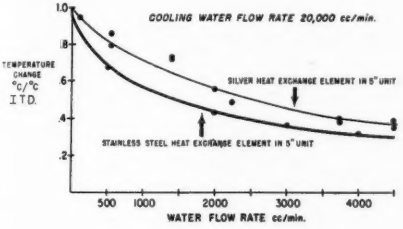

Fig. 3.

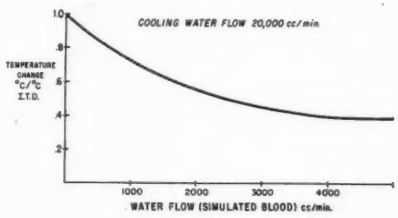

Fig. 4.

Fig. 3.—Test of stainless steel heat exchange element in comparison with a silver heat exchange element of an identical thickness.

Fig. 4.—Test of one 10-inch disposable heat exchanger (95 c.c. prime) indicates it is equal in efficiency to two Harrison-Brown units (330 c.c. prime) in series or one Pemco unit (450 c.c. prime).

is shown plotted in Fig. 3. Silver has twelve times the thermal conductivity of stainless steel; however, replacing the stainless steel element with a silver element produces an increase in heat transfer equivalent to doubling the length of the unit in stainless steel as may be seen by comparing the heat exchange curve for the 10 inch unit shown in Fig. 4 with the curve on the 5 inch silver unit shown in Fig. 3. The 10 inch unit with a silver heat exchange element would theoretically equal the heat transfer ability of four Harrison-Brown units. We have not fabricated this unit for test as yet. A study of the economics of complete stainless steel units versus complete silver units indicated that the use of silver would actually reduce cost of a disposable unit since silver can be reclaimed at 90 per cent of its original value, whereas used stainless steel has relatively little value. Brazing problems have been more difficult in the silver unit, however, and the superior mechanical properties of stainless steel have caused us to select this metal as ideal for the purpose.

A study of the effect of water flow rates on the efficiency of the cooling process has been previously reported.[14] The highest flow rates attainable will result in the best heat transfer, and it has been standard practice to employ a flow as high as 20,000 c.c. per minute. An efficient ice water circulating apparatus has been devised which is capable of holding 150 pounds of flake ice (Fig. 5) in order that one filling will suffice for cooling an adult patient

and recooling if necessary. Melting has been no problem during standby service because of the large size of the unit. Rewarming water at 42° C. is secured from a wall-mounted Powers regulator valve.

The units have practically no resistance to flow, up to a blood flow of 2 L. per minute. Gentle turbulence then begins and resistance gradually rises to a maximum of 15 mm. Hg at 4 L. per minute of blood flow. The unit can be

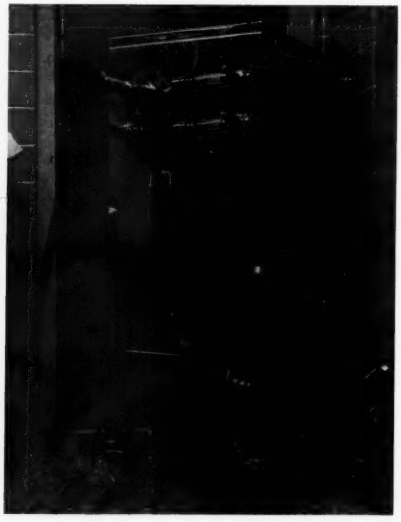

Fig. 5.—Large ice water circulating tank is equipped with three corrosion proof circulating pumps. Snap-Tite hose couplings are used for quick coupling of hoses and contain automatic valves that close on disconnecting to keep floor dry. A 5-inch heat exchanger can be mounted on the tank for isolated circuit local gastric hypothermia.

used, therefore, in the venous syphon line into the oxygenator. Hemolysis studies at 4 L. per minute flow have disclosed no measurable hemolysis due to the unit.[14] The unit acts to depulsate partially the low hemolysis, 360 degree, single roller, spring-loaded blood pump used and further reduces the already negligible hemolysis of the system. We have found that a position between the plastic disc oxygenator[15] and the 360-degree pump[16] on the mechanical drive is most convenient (Fig. 6), although we have also employed the exchangers in the high pressure side of the circuit (Fig. 7). Laboratory tests have shown that the exchangers will withstand city water pressure without leakage, and no difficulty has been experienced with the units in the arterial line. A unique feature of the design of the disposable exchanger is that all seals are external. Water and blood can only leak out into the room and not into the opposite compartment. The device is therefore "fail safe" in design although careful assembly and testing insures that all units are free of pinhole leaks.

Blood and water are run countercurrent through the exchanger for maximum efficiency, although at very high flow rates of water the benefits of this technique are minimal.

An efficient heat exchanger can be seriously compromised if it is employed in one of a number of ways. A maximum flow of 0° C. water or –2° C. brine is necessary to attain maximum cooling efficiency. The simplest way in which to realize this is to employ flake ice and a centrifugal recirculating pump at the highest practical flow rate attainable. As Count Rumford discovered many years ago when boring cannon barrels, the energy of mechanical motion is easily and inevitably converted into molecular motion we call heat. The rotation of a centrifugal pump in ice water will raise the temperature of the

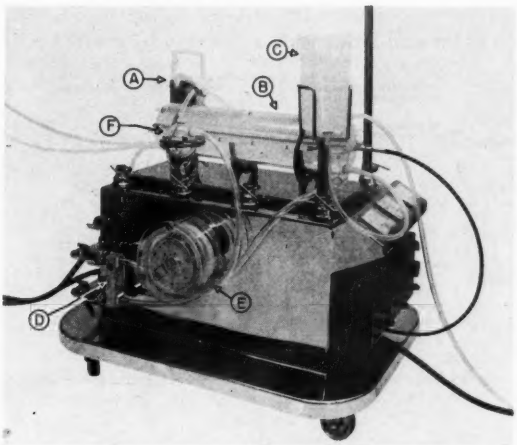

Fig. 6.—A 5-inch exchanger *(D)* is shown mounted on the mechanical drive unit between the oxygenator *(B)* and 360-degree, single roller, spring-loaded pump *(E)*. An efficient bubble trap *(F)* is shown mounted distal to the pump in the arterial line. The open-heart suction return reservoir *(A)* and the oxygenator reservoir *(C)* are shown mounted on the unit.

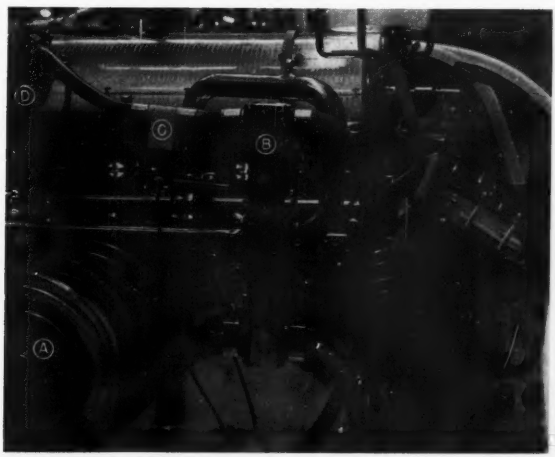

Fig. 7.—A 10-inch disposable heat exchanger *(B)* is shown mounted between the 360-degree pump *(A)* and bubble trap *(D)*. The thermistor arterial temperature probe *(C)* is visible between the exchanger and bubble trap.

water slightly and the most efficient application of a centrifugal recirculating pump is to employ it to return the effluent cooling water to the ice tank after it has passed through the heat exchanger by gravity through an insulated hose line of the shortest possible length. We have not considered this an important factor in attaining mid-esophageal temperatures of 10° C., but if we desire to cool to 5° C. or even 1° C. at some time in the future, this method will be employed.

If a single sump and syphon is employed to drain systemic and coronary blood from the right atrium, and if drainage is inefficient and right atrial pressure is maintained at a high level, part of the blood will continue to be circulated by the heart and will result in a delay in perfusion of the brain with

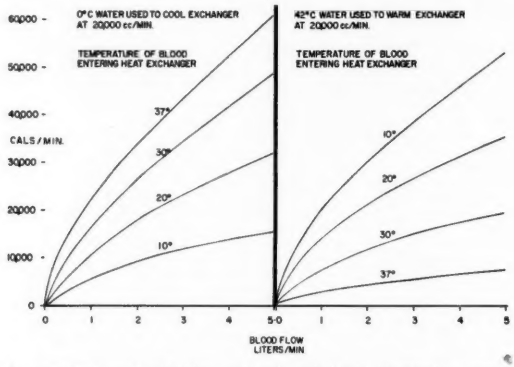

Fig. 8.—Caloric removal and addition with the 10-inch disposable exchanger. The higher the flow rates at a given input temperature, the more calories will be removed per minute. The lower the input temperature of the blood into the exchanger the fewer total calories that can be removed per minute. This general pattern is true of all heat exchangers.

cold blood. Right atrial pressure should be reduced to 0 mm. Hg by employing a sump of sufficient size, tubing of sufficient internal diameter, and a syphon height sufficient to insure complete bypass of the heart from the very inception of the induction of hypothermia.

If the exchanger is employed in the venous syphon line alone, when using an oxygenator system, the additional passage of blood through the room air-warmed equipment will moderately delay attainment of profound hypothermia. In addition, if a stainless steel disc oxygenator is used, large quantities of heat will be conducted into the blood via the stainless steel and, therefore, delay the attainment of the profound hypothermic state. The plastic disc oxygenator is ideal for this purpose since the coefficient of heat transfer for this plastic (methylmethacrylate) is over 500 times less than that of stainless steel.

In addition, if low flow perfusion of the patient is employed, a number of conditions unfavorable to efficient heat transfer arise. Any given heat exchanger transfers more and more heat, at any given cooling water temperature and flow, as the blood flow rate through the exchanger rises (Fig. 8). Low flow perfusion will then seriously reduce the quantity of heat removed from the patient by the blood passing through the heat exchanger.

Low flow perfusion results in low systemic blood pressure and, therefore, poor partitioning of blood flow to various areas of the body. Since blood is introduced usually via the femoral artery, significant warming will occur before reaching the brain and the diminished flow rate through the brain will result in poor heat transfer and the likelihood of a serious lag in brain temperature behind esophageal temperature. It is of great interest that Sealy[17] found esophageal temperatures to be much lower than brain temperatures in his low flow perfusion, whereas Gordon,[10] using high flow perfusions, found very excellent correlation. Full flow perfusion should be employed to cool to a mid-esophageal temperature of 10° C. if circulatory arrest is contemplated.

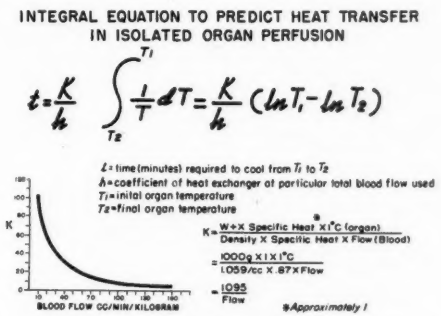
INTEGRAL EQUATION TO PREDICT HEAT TRANSFER
IN ISOLATED ORGAN PERFUSION
$t=\frac{K}{h}\int_{T_2}^{T_1}\frac{1}{T}dT=\frac{K}{h}(\ln T_1-\ln T_2)$
t = time (minutes) required to cool from T_1 to T_2
h = coefficient of heat exchanger at particular total blood flow used
T_1 = initial organ temperature
T_2 = final organ temperature
K
BLOOD FLOW CC/MIN/KILOGRAM
$K=\frac{W\div X\ \text{Specific Heat}\ X\ 1°C\ (\text{organ})}{\text{Density}\ X\ \text{Specific Heat}\ X\ \text{Flow (Blood)}}$
$=\frac{1000g\ X\ 1\ X\ 1°C}{1.059/cc\ X\ .87\ X\ \text{Flow}}$
$=\frac{1095}{\text{Flow}}$
Approximately 1

Fig. 9.—The time required to cool an isolated insulated individual organ can be predicted from this simple integral.

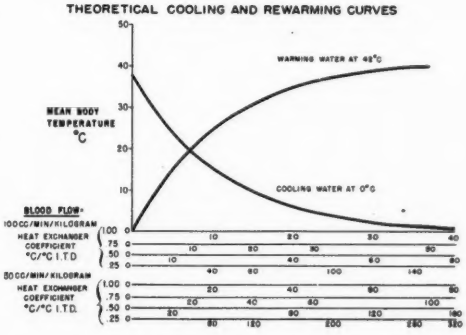

Fig. 10.—If the body were uniformly perfused, the time required to reach 10° C. average temperature would be considerable, even with a perfect heat exchanger (coefficient = 1.00).

Although cooling and rewarming calculations for isolated, insulated, individual organs are not difficult (Fig. 9), calculations involving a body which has a multiplicity of organs, having different flow rates per unit weight of tissue and thermal change due to conduction of heat, present a formidable mathematical problem which is now under study. We know from our own studies and the work of Sealy[17] and Gordon[10] that the muscle masses may remain at temperatures between 20° and 30° C. while the mid-esophageal temperature drops to 10° C. A 70-kilogram adult has approximately 6

TABLE I. TOTAL OF 17 CONSECUTIVE PATIENTS OPERATED UPON UNDER PROFOUND HYPOTHERMIA, TO DATE

AGE (YR.)	WEIGHT (LB.)	DIAGNOSIS	RESULTS	TIME TO COOL TO 15° C. (MIN.)	LOWEST MID-ESOPHAGEAL TEMP.	TIME TO REWARM TO 35° C. (MIN.)	TYPE HEAT EXCHANGER	DURATION OF CIRCULATORY ARREST (MIN.)	ARTERIAL pH			
									BEFORE COOLING	LOWEST TEMP.	AFTER WARMING	POSTOP. 2 HR.*
11	70.5	IASD + IVSD + tricuspid stenosis	Died*	15	12	47	1 - 5 in.	63	7.56	7.47	7.40	—
26	92	IVSD + pulmonary hypertension	Died†	22	10	29	1 - 5 in.	No arrest	7.42	7.36	7.42	—
6	41	IVSD + pulmonary hypertension	Died†	15	10	28	1 - 5 in.	No arrest	7.61	—	7.47	—
7	42	IVSD + PDA	Living and well	17	11	33	1 - 5 in.	No arrest	7.67	7.54	7.51	7.46
33	136.5	MS + MI	Died‡	39	12	87	2 - 5 in.	No arrest	7.48	7.43	7.38	7.42
2	26	IVSD + IPS	Living and well	13	13	22	1 - 5 in.	No arrest	7.58	7.52	7.54	7.43
37	104	MS + MI	Died‡	16	10	40	2 - 5 in.	42	7.50	7.39	7.39	—
13	72	IASD + anomalous venous drainage	Living and well	4	9	6	1 - 5 in. + 1 Pemco	47	7.67	7.38	7.61	7.50
39	120	MS	Living and well	14	10	29	1 - 5 in. + 1 Pemco	47	7.60	7.61	7.57	7.57
5	37.25	IVSD	Living and well	17	13.7	31	1 Pemco	No arrest	7.64	7.60	7.50	7.43
13	86	IASD primum with cleft mitral valve	Living and well	8	11	28	2 - 5 in.	65	7.63	7.44	7.66	7.48
23	134	IPS	Living and well	10	10.6	25	1 - 10 in.	40	7.57	7.60	7.55	7.42
34	162	IVSD + PS	Living and well	16	11	27	1 - 10 in.	29	7.58	7.56	7.42	7.40
4	34.25	IVSD	Living and well	13	13	23	1 - 5 in.	40	7.70	7.31	7.48	7.43
5	37.5	Tetralogy of Fallot	Living and well	16	7.8	26	1 - 5 in.	48	7.53	7.24	7.42	7.44
3	24.75	IVSD	Living and well	5	9.5	27	1 - 5 in.	21	7.47	7.25	7.44	7.43
3	29.75	IASD	Living and well	8	9.5	21	1 - 5 in.	20	7.49	7.42	7.40	7.40
Averages				14.58	10.77	31.12		41.64	7.57	7.45	7.48	7.45

Legend: IASD—Interatrial septal defect. IVSD—Interventricular septal defect. PDA—Patent ductus arteriosus. MS—Mitral stenosis. MI—Mitral insufficiency. IPS—Infundibular pulmonic stenosis. PS—Pulmonic stenosis.

*Uncorrectable lesion with rudimentary right ventricle.

†Pulmonary hypertension resulted in insufficient blood flow after surgery with marked arterial unsaturation.

‡Patients in congestive failure prior to operation. Mitral valve severely calcified and inoperable in both cases.

kilograms of vital organs and 64 kilograms of muscle, bone, skin, fat, and connective tissue. Of the 5,200 c.c. per minute basal blood flow, 4,200 c.c. per minute goes to the 6 kilograms of vital organs and only 1,000 c.c. per minute to the muscle, bone, skin, fat, and connective tissue. Since temperature difference, flow, and time are all required to move a given quantity of heat, it is not surprising that core cooling results so efficiently. If the entire body had to be cooled to an average temperature of 10° C., the time required would be prohibitively long (Fig. 10).

Following extensive laboratory testing on 35 dogs, which proved the efficiency and safety of the units, and after extensive toxicity testing which was completely negative, we have employed disposable heat exchangers clinically to induce and recover from profound hypothermia with complete success. Performance has been predictable, and no difficulty has been experienced in its use with the largest patients. The units have been employed at all times in the oxygenation system shown in Fig. 6. Seventeen patients comprise this series and are tabulated in Tables I and II.

TABLE II. BLOOD CHEMISTRIES IN THE LAST 10* CONSECUTIVE PATIENTS HAVING OPEN-HEART SURGERY UNDER PROFOUND HYPOTHERMIA

	CO_2 (VOL. %)				LACTIC ACID (MG. %)			PYRUVATE (MG. %)		
	PRE-PUMP	LOWEST TEMP.	AFTER WARMING	2 HR. POSTOP.	PRE-PUMP	LOWEST TEMP.	AFTER WARMING	PRE-PUMP	LOWEST TEMP.	AFTER WARMING
IVSD + anomalous venous drainage	30.81	53.5	31.81		10.53	16.33	21.42	0.488	0.465	0.500
MS	39.19	39.07	37.81	43.75	23.30	26.48	27.54	0.206	0.065	0.373
IASD primum with cleft mitral value	37.75	41.5	41	44.50	31.52	38.04	52.17	0.205	0.614	0.241
IPS	38.69	50.81	43.52	44.03	43.65	36.92	37.5	0.045	0.139	0.161
IVSD + PS	42.91	52.08	45	42.42	41.82	43.12	32.34	0.115	0.160	0.130
IVSD	37.87	44.79	39.84	45.57	32.94	15	27.65	0.289	0.440	0.542
Tetralogy of Fallot	39.6	65.7	50.12	44.28	56.47	38.82	32.35	0.217	0.554	0.416
IVSD	42.1	55.9	41.67	34.65	29.41	30.88	44.12	0.100	0.100	0.253
IASD	31.64	54.74	34.00	38.75	29.35	31.52	36.09	0.181	0.169	0.337
Averages	37.74	49.26	41.58	42.08	33.18	31.08	32.65	0.205	0.301	0.323

For legend see Table I.
*Complete chemistries were not determined on the first 7 cases.

Fluothane anesthesia was used in all cases. All patients were digitalized prior to operation except one.[18] Following the induction of general anesthesia, the patient was placed on the operating table on a Thermo-Rite blanket, and slow cooling was begun. At the time of bypass, mid-esophageal temperatures ranged about 32° C. The 13 inch (or 22 inch) plastic disc oxygenation system was primed with 5 (or 7) pints of fresh heparinized blood containing 1,500 units of heparin per pint, and the blood was slowly recirculated and the lines cleared of all bubbles. Oxygenation was begun with a mixture of 95 per cent O_2 and 5 per cent CO_2 in the oxygenator. In some instances the blood was precooled in the perfusion apparatus to 10° C. before starting bypass. In other instances no effort was made to cool the blood until bypass was instituted. The flow rate for the particular patient was selected from the

‡Patients in congestive failure prior to operation. Mitral valve severely calcified and inoperable in both cases.

curves of Leland Clark[19] on optimum flow rates and varied from about 50 c.c. per kilogram per minute in adults to 100 c.c. per kilogram per minute in children. Lately we have been placing ice bags over the eyes to precool the vitreous humor since it is avascular and cannot be cooled effectively by perfusing the retina. The retina, being essentially an extension of the central nervous system, probably possesses the same high level of metabolic activity as the brain itself and must be protected. A simple sump drainage catheter was placed in the right atrium, and the arterial inflow catheter was introduced

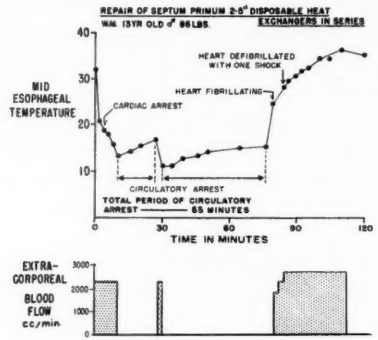
REPAIR OF SEPTUM PRIMUM 2-5° DISPOSABLE HEAT EXCHANGERS IN SERIES
WM. 13YR OLD ♂ 86 LBS.
MID ESOPHAGEAL TEMPERATURE
HEART DEFIBRILLATED WITH ONE SHOCK
HEART FIBRILLATING
CARDIAC ARREST
CIRCULATORY ARREST
TOTAL PERIOD OF CIRCULATORY ARREST — 65 MINUTES
TIME IN MINUTES
EXTRA-CORPOREAL BLOOD FLOW cc/min.

Fig. 11.

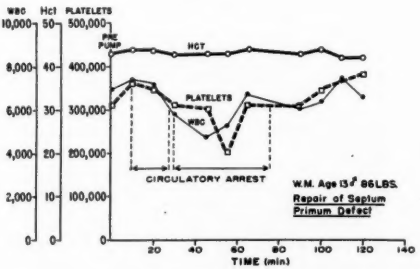

Fig 12.—Hematology of pump blood during cooling and rewarming.

into the femoral artery. At the start of perfusion, the precalibrated, occlusively set, 360-degree spring-loaded pump was begun at the required flow rate and oxygenator disc speed was adjusted. Arterial pressure was monitored by a Statham strain gauge from the brachial artery and central venous pressure with a similar gauge in the inferior vena cava. Adjustment in flow was rarely required and after the ice water had begun circulating through the heat exchanger, mid-esophageal temperature fell rapidly and reached 20° C. in an average of 8.5 minutes and 15° C. in 14.6 minutes.

Since the form of the cooling and rewarming curve is exponential, it is incorrect to say that cooling is so many degrees per minute since the initial temperature fall is rapid, but the last degree of fall sometimes takes several minutes. If an attempt is made to reach temperatures less than 10° C., the

fall in temperature usually ceases at 7° to 8° C. in complete thermal equilibrium with the room, which is adding heat at this low temperature as fast as the heat exchanger can remove it. The addition of cold brine for ice water at this point will lower the temperature slightly until a new thermal equilibrium point is realized.

Rewarming to a mid-esophageal temperature of 35° C. has required slightly more than double the time required to cool to 15° C. This can be partially explained (see Fig. 8) by the smaller temperature differentials

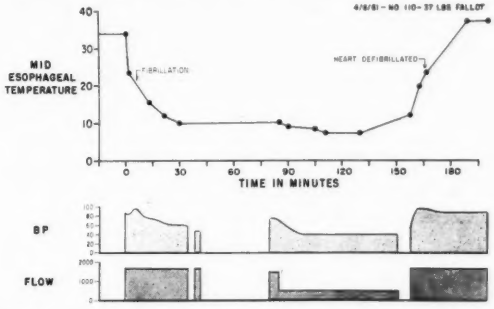

Fig. 13.—Repair of tetralogy of Fallot in a 37-pound male (April 6, 1961).

obtained during rewarming when using water at 42° C. Another factor retarding rewarming is the lessened blood flow through the cold muscle mass which allows rapid core rewarming initially but which acts to retard the completion of the rewarming process.

The longest period of circulatory arrest in one of our patients was 65 minutes, and this was divided into two periods with a short 3-minute period of recirculation between them. Fig. 11 is a record of the cooling of this 13-year-old patient, circulatory arrest and repair of a septum primum defect and rewarming with two 5-inch disposable heat exchangers. Fig. 12 shows hematologic data secured in the same patient. A slight fall in white cells and platelets is seen but nothing like the decrease reported by Björk.

The lowest temperature recorded on a clinical patient was a mid-esophageal temperature of 78° C. during a long and difficult 3-hour repair of a tetralogy of Fallot (Fig. 13).

No postoperative acidosis was experienced in any patient and there was no postoperative arterial pH below 7.4 except in one patient with one of 7.38 which rose to 7.42 2 hours postoperatively. Patients awoke promptly after operation. No bicarbonate infusion was necessary in any patient. The absence of neurologic change in these patients will be the subject of a future report.

SUMMARY

A safe, efficient, low cost, disposable stainless steel heat exchanger has been designed which is an efficient instrument for the induction and recovery from profound hypothermia. Since postoperative acidosis is completely absent from

this series of patients, it is suggested that the plastic disc oxygenator is more efficient than the human lung at low temperatures and that high arterial blood oxygen tension may actually be desirable in these patients as a more readily available source of oxygen than that which is bound to hemoglobin. Factors influencing the efficiency of the cooling and rewarming process have been discussed.

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(For Discussion, see page 637.)

GAS CHROMATOGRAPHY: A SIMPLE, RAPID, RELIABLE METHOD FOR BLOOD GAS ANALYSES

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Gas chromatography is the first reliable method for blood gas analysis that has been introduced since the classical contributions of Van Slyke, Neill, and Sendroy[1, 2] in the 1920's. Oxygen and carbon dioxide analyses that formerly required hours of monotonous labor can now be determined more accurately with gas chromatography in 5 to 10 minutes.

Basically, gas chromatography consists of a two phase system whereby a sample of gas or liquid is introduced into a carrier gas stream. The sample is transported into the chromatographic column (fixed phase) and washed through by the continuous flow of carrier gas (mobile phase). Since components in the sample will travel through the column packing at a rate dependent on the individual adsorption coefficients, each component will emerge from the end of the column at a different time (Fig. 1). As the components emerge, they are detected and measured individually by a thermal conductivity cell. The output of this detector is then indicated on a recorder by a series of peaks, the area under each peak being proportional to the concentration of the component producing it. Thus, with suitable calibration, peak height also provides a measure of concentration. A new sample can be introduced immediately after the last component leaves the column, since the flushing action of carrier gas sweeps the column clean.

METHOD

The Beckman GC-2 and Consolidated 26-201A Chromatographs were easily modified for routine laboratory use. These modifications include the placement of an analytical cuvette, with a 0.5 ml. pipette attached to it, into the carrier gas stream. The top of the pipette is connected to a manifold which has compressed air for delivering blood to the cuvette, an open chamber for measuring the volume of blood delivered at the ambient pressure, and suction for cleansing the pipette (Fig. 2).

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The first step in the procedure is the introduction of 2 ml. of a 1:1 solution of a saponin-potassium ferricyanide and 0.5 N lactic acid, plus 0.2 c.c. of Antifoam 60* into the chamber. Deaeration is performed by passing helium through the chamber until the chromatographic curve returns to the base line.

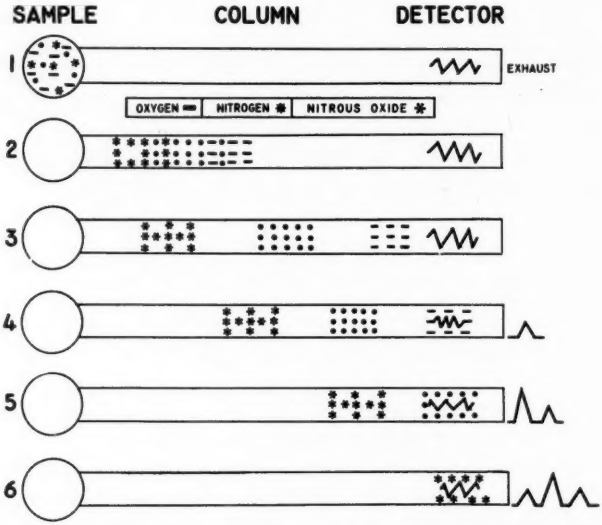

Fig. 1.—Three component samples consisting of oxygen, nitrogen, and nitrous oxide flowing into the adsorption column where they are separated and detected individually as they emerge. (Courtesy of Consolidated Electrodynamics Corp., Pasadena, Calif.)

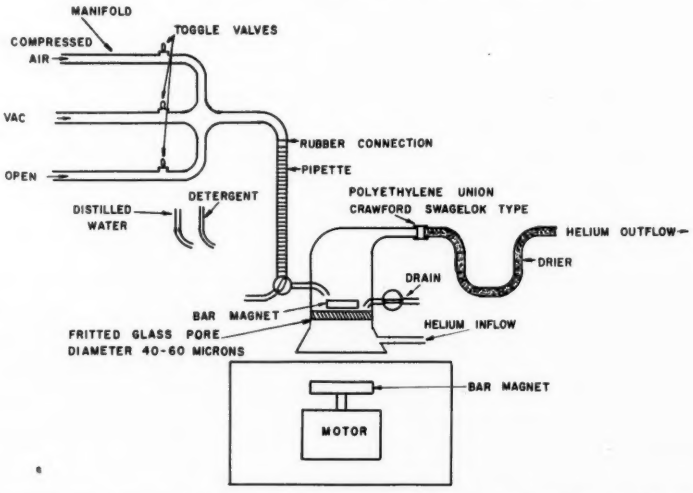

Fig. 2.—Pyrex glass analytical cuvette with manifold attached to pipette, indicating anhydrous calcium sulfate is the drying agent.

*General Electric Co., Schenectady, New York.

The pipette is then filled with blood from a mercury-sealed syringe through the 3-way stopcock at the bottom of the pipette, with the manifold open to room air. The level in the pipette is then read to the thousandth of a milliliter. The sample of blood is delivered to the deaerated analytical chamber with compressed air pressure from the manifold. When this is completed, the manifold is again opened to room air and the blood allowed to settle in the pipette for 4 minutes before determining the volume of the sample delivered to the cuvette.

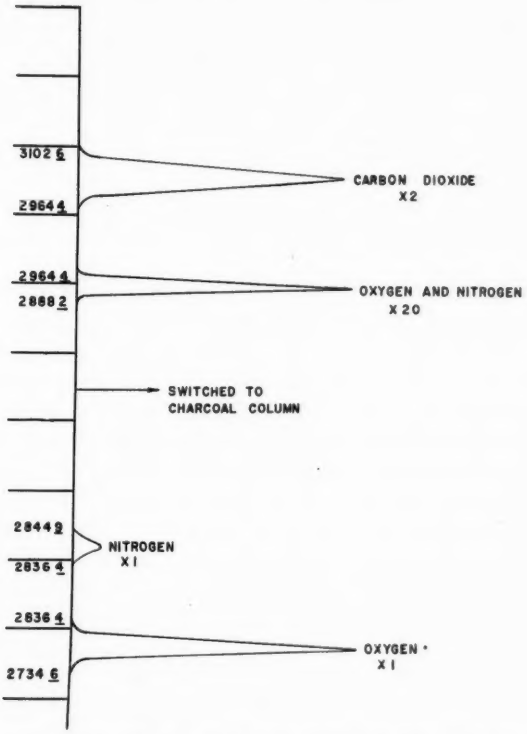

Fig. 3.—Copy of curves obtained during an analytical procedure on sample of whole blood. Numbers at the bottom were printed by the integrator. The difference between the numbers on either side of peaks represents the area in arbitrary units. Time sequence is from bottom to top.

In the meantime the carrier stream of helium now picks up the gases liberated in the cuvette and carries them through the sampling valve and into a column 120 inches in length that contains 30 to 60 mesh molecular sieves. This column holds the CO_2 indefinitely and resolves the oxygen and nitrogen. The oxygen is followed by the nitrogen as it leaves the column and passes into the thermal conductivity cell where the output of the detector records the peaks. To obtain resolution of the CO_2 from the oxygen and nitrogen, a second sample of blood is injected into the cuvette and the gases then allowed to traverse an

18-inch column of activated charcoal. Fig. 3 is an actual recording of the peaks as they evolve from the two columns. The areas under the curves were integrated with a recording integrator.*

The quantity of oxygen or carbon dioxide expressed in milliliters per 100 ml. of blood were calculated in the following way:

$C_{B_{O_2}}$ or $C_{B_{CO_2}} = (V_L/V_B) \times Fs_{O_2}$ or $Fs_{CO_2} / (A_s \times A_u)$

$C_{B_{O_2}}$ or $C_{B_{CO_2}} = O_2$ or CO_2 content in blood in volumes per cent.

V_L = Volume of sampling loop in gas chromatograph corrected to standard temperature, pressure, dry.

V_B = Volume of blood injected into analytic chamber.

Fs_{O_2} or Fs_{CO_2} = Known volume per cent of O_2 or CO_2 used in calibration procedure of standard gas sample.

A_s = Area under curve obtained when standard containing known content of O_2 or CO_2 was analyzed.

A_u = Area under curve obtained when blood sample was analyzed for unknown content, O_2 or CO_2.

More detailed information of this method may be found in the work of Jay and Wilson,[3] and Wilson, Jay, Doty, Pingree, and Higgins.[4]

RESULTS

The chromatographic method of analyzing blood for oxygen and carbon dioxide was compared with that of Van Slyke and Neill. Table I summarizes the data obtained from the analyses of aliquots of the same blood sample for oxygen with both methods. The samples were obtained from 15 different persons. The average difference between the two methods was 0.19 vol. per cent. The t test for null hypothesis revealed no significance of difference. Table I also summarizes the data for comparison of the carbon dioxide analysis of whole blood. There was a significant difference between the average values obtained with the two methods ($p < 0.01$).

TABLE I. SUMMARY OF ANALYSIS OF WHOLE BLOOD*

STATISTIC	BLOOD GAS	CHROMATOGRAPH (VOL. %)	VAN SLYKE (VOL. %)	SIGNIFICANCE
S.D. of replicates	O_2	±0.0378	±0.0366	N.S.
	CO_2	±0.0366	±0.0371	N.S.
Mean difference between methods	O_2	0.1947		N.S.
	CO_2	1.3910		$p < 0.01$

*Analysis of whole blood done by method of Van Slyke and Neill[2] and Van Slyke and Sendroy[1] and the gas chromatograph.

This difference prompted us to analyze a 0.018 M solution of sodium carbonate for its CO_2 content with both methods. The gas chromatograph was not significantly different from the calculated value of 40.32 vol. per cent carbon

*Perkin-Elmer Co., Norwalk, Connecticut.

dioxide in the solution of sodium carbonate (Table II). There was a significant difference, however, between the calculated CO_2 value of the 0.018 M solution of sodium carbonate and the method of Van Slyke and Sendroy. The degree of difference was of the same magnitude as with arterial blood and represents an inherent error in the Van Slyke procedure whereby all of the CO_2 was either not released or was reabsorbed into the solution before the time of reading.

TABLE II. SUMMARY OF RESULTS OF ANALYSIS OF SODIUM CARBONATE*

STATISTIC	VAN SLYKE AND SENDROY[1] (VOL. %)	GAS CHROMATOGRAPH (VOL. %)	
Mean	38.31	40.35	Theoretic amount of CO_2 in 0.018 M solution of Na_2CO_3 is 40.32 vol. %
S.D.	±0.17	±0.085	
Mean difference from theoretic value	2.008	±0.025	
Significance of difference from theoretic value	$p < 0.01$	N.S.	

*Analysis of an 0.018 M solution of sodium carbonate with two methods and a statistic comparison with theoretic yield of CO_2 from known solution.

CONCLUSIONS

1. A simple, rapid, reliable method of blood gas analysis with gas chromatography is described.

2. There was no statistically significant difference between the Van Slyke and gas chromatographic analyses for the oxygen content of whole blood.

3. Carbon dioxide analyses of whole blood and 0.01814 solution of sodium carbonate revealed a significant defect in the Van Slyke method.

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(For Discussion, see page 637.)

A NEW REFLECTION OXIMETER

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A simple and reliable method of determining blood oxygen has long been sought by both investigators and clinicians. Variations in this important body parameter can only be determined by crude clinical appraisal or time consuming laboratory procedures. The advent of cardiac catheterization and cardiopulmonary bypass has intensified study of blood gas determinations.

Oximetry has been applied to this problem in recent years by a number of men. The development of the "Haemoreflector" by Brinkman and Zijlstra[1] in 1949 demonstrated the importance of reflection oximetry in monitoring oxygen saturation. Oximeters to date have been difficult to standardize and calibrate. Drift has occurred with wide variations, particularly in the lower ranges of oxygen saturation. In essence, oximetry to date has never become the helpful adjunct to the clinical care of the patient envisioned by its proponents.

This paper is based on 34 patients analyzed for oxygen saturation and other body constituents. These patients underwent procedures such as cardiac catheterization, open-heart surgery, bronchoscopy, and thoracotomy. In all some 282 blood samples were compared by reflection oximetry and standard spectrophotometric procedures. In addition, 100 blood samples were compared by manometric techniques and reflection oximetry.

The instrument we have used is a new type reflection oximeter* developed by Polanyi and Hehir.[2]

THEORY

In spectrophotometric techniques, oxygen saturation is obtained from the optical density of a hemolyzed sample of blood measured at two appropriate wave lengths. One of these wave lengths is an isosbestic point for oxidized and

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*Instrument developed and built by Research Division American Optical Company, Southbridge, Mass.

reduced hemoglobin.[3] The saturation can then be determined from a well-known linear relationship, example, Equation 1:

Equation 1: $O.S. = A_t + B_t \times [O.D.\ (\gamma_1)/O.D.\ (\gamma_2)]$

Where $\gamma_1 = 650$ mμ, $\gamma_2 = 805$ mμ, and A_t and B_t are functions of the extinction coefficients of oxyhemoglobin and reduced hemoglobin at these two wave lengths.

To compare the oxygen saturation determined with reflection oximetry against other methods, the same samples were also analyzed by spectrophotometric procedures[4] and by manometric techniques employing the method of Van Slyke and Neill.[5, 6] Oxygen capacity used in determining the saturation from Van Slyke was determined on a Beckman D.U. spectrophotometer.[7] The pH meter used throughout the study was a Model G, Beckman No. 2000, with appropriate corrections for temperature variation.[8] The carbon dioxide pressure was calculated using the method described by Leitner and Thaler.[9]

WHOLE BLOOD OXIMETRY

In dealing with whole blood, the determination of oxygen saturation using optical methods is complicated by the fact that whole blood is a highly diffusing medium to which Beer's Law, on which Equation 1 is based, does not apply. It is possible to correlate empirically the ratio of optical densities of unhemolyzed blood with oxygen saturation. Such oximeters have been built[10, 11] but the reported values indicate a definite inadequacy at lower oxygen concentrations. A clinically useful instrument should determine oxygen saturation within a wide range (40 to 100 per cent) of saturation with a standard deviation of ± 1 per cent.

The reflection oximeter of Zijlstra[12] is similar in some respects to the instrument used in this investigation. In his instrument the oxygen saturation is empirically correlated with the intensity of light diffusely reflected from a thick layer of whole blood. This instrument, as is the case with transmission oximeters, is deficient at lower oxygen levels and needs frequent calibration.

The basic difference is that our instrument utilizes two wave lengths. The ratio of light intensities scattered by the specimen observed at these wave lengths has definite advantages. (1) The instrument determines *absolute* values for oxygen saturation. No calibration is necessary. (2) Results are independent of light intensity, temperature, hemodilution, and cell size, shape, and origin.

The instrument used in this investigation is a reflection type of oximeter which uses unhemolyzed and undiluted blood. As shown in Fig. 1, it consists of a light source (tungsten lamp) focused on the flat portion of a cuvette containing the sample. The light diffusely reflected from the sample at about 45 degrees to the impinging light is measured by two photo cells. In front of each photo cell there is a filter (interference filter), one in the visible red spectrum 660 mμ and the other in the infrared 805 mμ. These filters limit the light reaching the photocells to wave lengths close to 660 mμ and 805 mμ, respectively. The light specularly reflected from the cuvette cannot reach the photocells due to

the geometry of the system. It should be noted that these two wave lengths are the same as those used in some of the standard spectophotometric methods (Beckman D. U.).[7]

The correlation between saturation and reflected light in this system is based on the fact that the back scattered light from the blood is inversely proportional to the extinction coefficients of the blood itself (Fig. 2). This has been shown by Rodrigo[13] in 1953 using one wave length (650 mμ) and Polanyi and Hehir[2] in 1960 employing a two wave length system. The ratio of the light intensity "seen" by the two photocells is measured electrically (by means

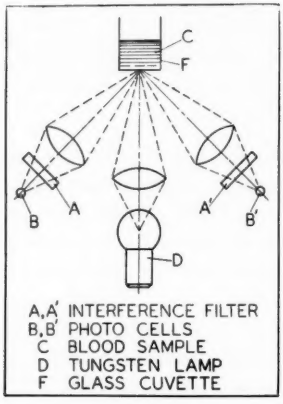

Fig. 1.

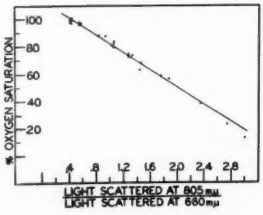

Fig. 2.

of a bridge circuit); this ratio, that is, the intensity scattered at 805 mμ divided by the intensity scattered at 660 mμ, is correlated with oxygen saturation. The oxygen saturation turns out to be a linear function. A complete description of this instrument has been published previously.[2] The basic theory of oximetry is beyond the scope of this paper. The articles of Zijlstra,[12] Wood,[14] and Comroe and Wood[15] are recommended.

Using the inverse relationship between back scattered light and extinction coefficients, Equation 1 can be rewritten as Equation 2.

$$\textit{Equation 2:}\ \text{O.S.} = A_t + B_t \times [I_r\ (\gamma_2)/I_r\ (\gamma_1)]$$

Where the values of A_t and B_t are the same as in Equation 1 and I_r refers to the back scattered light intensities at $\gamma_1 = 650$ mμ, $\gamma_2 = 805$ mμ.

PROCEDURE

1. There is a preliminary warm up time of 15 minutes. A flat "Vitrolite" reflection standard is now placed in lieu of the sample.
2. The potentiometer reading is set at a given value, and the instrument zeroed with the aid of a diaphragm.
3. The blood sample is transferred under the light mineral oil into a reflection cuvette and placed in the instrument. A rectangular flow cuvette is available for connection to the heart-lung pump.
4. A reading is made by adjusting the potentiometer to a null point on the meter. This usually requires about 15 seconds. Reference is then made to a prepared graph correlating potentiometer readings to oxygen saturation.
5. As an added precaution against drift, the standard is again reinserted and the null point checked.
6. Readings should be done promptly after mixing (within 15 seconds) to minimize rouleaux formation. Mixing of the sample is more critical at lower saturation levels. The sample in a manual cuvette will keep for at least 2 hours and readings can be repeated with ± 0.5 per cent oxygen saturation.

EXPERIMENTAL RESULTS

In all, 282 samples were measured simultaneously with the reflection oximeter and the Beckman D.U. spectrophotometer. In addition, about 100 of the same samples were also measured by the Van Slyke method. The results of the series of control experiments are summarized in Tables I and II. Under the column M are listed the average difference between the instruments compared. In Table I the standard deviation for 282 samples is 1.39 per cent oxygen saturation (reflection oximeter vs Beckman D.U.). This should be compared to the standard deviation of 1.69 per cent oxygen saturation in Table II for approximately 100 samples, comparing the Van Slyke with Beckman method. Furthermore, the results of the oxygen saturation determined by the standard methods as compared with those obtained with the present reflection oximeter have been plotted and they are illustrated on Fig. 3. It should be noted that part of the scatter about the 45 degree line is due in part to the experimental errors inherent in the standard procedure.

TABLE I

SERIES	PROCEDURE	NO. OF CASES	TOTAL PER CENT O.S.–R.O.*	TOTAL PER CENT O.S.–D.U.	NO. OF SAMPLES ANALYZED	AVG. M (% O.S.)	AVG.–S.D. (% O.S.)
I	Open-heart	7	5870.79	5871.75	71	0.317	1.39
II	Catheterization	11	8887.09	8944.75	113		
III	Arterial blood gas studies	5	443.50	442.50	5		
IV	Thoracic cases	10	8738.35	8737.65	93		

* Control experiments comparing oxygen saturation determined with reflection oximeter and Beckman D. U. spectrophotometer.

TABLE II

SERIES	PROCEDURE	NO. OF CASES	TOTAL PER CENT O.S.–R.O.*	TOTAL PER CENT O.S.–V.S.	NO. OF SAMPLES ANALYZED	AVG. M (% O.S.)	AVG –S.D (% O.S.)
I	Open-heart	7	1665.25	1675.75	20		
II	Catheterization	11	1016.25	1029.75	13		
III	Arterial blood gas studies	6	446.15	442.50	5	0.360	1.69
IV	Thoracic cases	10	5774.75	5800.75	61		

*Results of same series comparing two standard procedures: Van Slyke vs Beckman D.U.

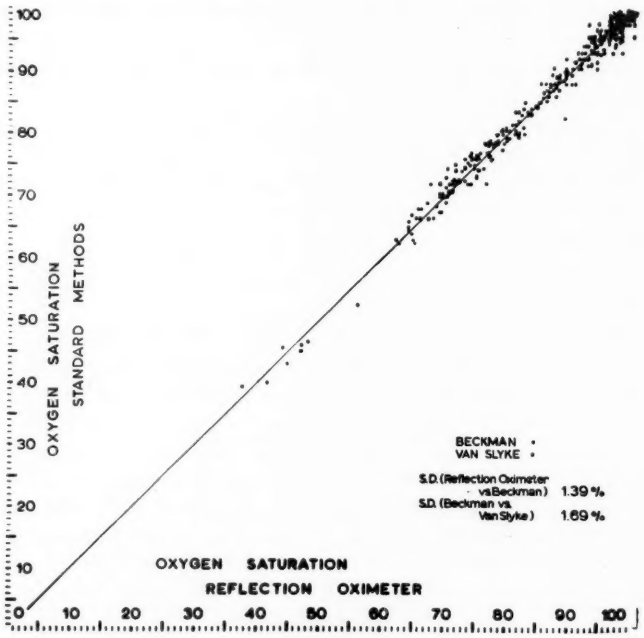

Fig. 3.

In evaluation of the two standard methods, Van Slyke vs Beckman D.U., (Table II) we must bear in mind that the reflection oximeter does not influence the standard deviation of 1.69 per cent oxygen saturation. This standard deviation is similar to values obtained by other investigators comparing the same two instruments.

It is safe to conclude that there is no significant difference in the standard deviations in Tables I and II and that the three methods in this investigation, i.e., Van Slyke—hemolyzed blood, Beckman D.U.—hemolyzed blood, reflection oximeter—whole blood, can be used with equal confidence in the determination of oxygen saturation.

The values obtained in Tables I, II, were determined with the following formulas:

I.

$$M = \frac{\sum_{1}^{n} (y_1 - y_2)}{n}$$

II.

$$S = \frac{\sqrt{\Sigma\{M - (y_1 - y_2)\}^2}}{n - 1}$$

III.

$$r = \frac{\Sigma\, y_1 \cdot y_2}{\sqrt{\Sigma\, (y_1)^2 \cdot \Sigma\, (y_2)^2}}$$

Formula I. M = Mean deviation. Formula II. S = delta:standard deviation. Formula III. r = coefficient of correlation; y_1 = observed value R.O.; y_2 = observed value standard method; n = no. sample.

DISCUSSION

The possible clinical uses of a simple, reliable, and rapid oximeter are nearly endless. The intubation and extubation of patients are known to be critical periods. Similar situations may arise during endoscopy and tracheostomy. In apnea occurring for any reason, such as during electroshock therapy, breath-holding during anesthesia, larngospasm, and the like, it would be most helpful to quickly ascertain the level of oxygen saturation. The availability of bedside monitoring of oxygen saturation guides therapy in the care of patients with myocardial infarcts, bronchial asthma, postoperative atelectasis, or chronic obstructive emphysema, A reflection oximeter, during cardiac catheterization, permits rapid evaluation of numerous blood samples. In this way a dynamic evolution of diagnosis can occur while the study is actually in progress. In actual practice the diagnosis is usually made or at least shrewdly suspected before the catheter is removed. Oxygen saturation, quickly determined, may be valuable during pulmonary or closed heart operations. Rapid, accurate determinations of oxygen saturation during cardiopulmonary bypass are essential.

Our present oximeter can be used in many ways. A small auxiliary pump or syringe can be used for flow with an indwelling needle or catheter. In actual practice we have utilized mainly an indwelling Cournand arterial needle and withdrawn individual blood samples as indicated for ready analysis in a manual-type cuvette. Frequent monitoring, in patients with limited pulmonary reserve undergoing bronchoscopy, or thoractomy, may be very revealing. Frequent determinations of saturation with the instrument during open thoractomy in such patients and, in particular, in the recovery room has been helpful in clinical management. Thoracic surgeons are well aware of the inherent dangers in the emphysematous patient with an inflammatory lesion who requires a thoracotomy. The inevitable blood loss may require multiple transfusions. Such a patient, even with a tracheostomy and assisted ventilation, may very well

die in the immediate postoperative period. The critical time comprises the immediate postoperative hours in the recovery room and intense care unit. Logical postoperative care is greatly facilitated by an instrument which will give a bedside determination of oxygen saturation. If this is combined with a pH determination and carbon dioxide content, then one has a very accurate estimate of the patients physiologic and chemical status.

There are many parameters to ensure safe total body perfusion. The oxygen saturation of arterial and venous blood is certainly one of the more basic for the safety of the patient. The venous saturation, in particular, is important since this really reflects what has occurred during perfusion of a particular

TABLE III

SAMPLE	REMARKS	% SAT. BECKMAN	% SAT. R.O.	% SAT. VAN SLYKE	pco_2 (mm. Hg)	pH	Hct.
	Case 1. E.S.—56 years—Left Upper Lobectomy						
1	Pre-anesthesia	89.5	89.0	86.8	34.2	7.42	40
3	Intubation	93.0	92.0	94.0	51.0	7.28	36
4	Intubation	96.5	96.5	93.8	46.4	7.30	35
6	Incision	98.5	96.6	96.25	52.7	7.26	34
7	Chest open	94.0	92.5	96.8	53.2	7.25	38
8	Post-suction	91.0	92.5	91.3	49.7	7.25	35
10	Post-suction	97.5	97.0			7.26	37
11	Chest closed	95.0	93.5		50.0	7.32	41
12	Extubation	83.5	83.0	81.5	43.6	7.32	39
13	Recovery room—1 hr.	93.0	94.0	90.8	42.4	7.36	34

TABLE IV

SAMPLE	REMARKS	% SAT. BECKMAN	% SAT. R.O.	% SAT. VAN SLYKE	pco_2 (mm. Hg)	pH	Hct.
	Case 2. R. F.—67 years—Pulmonary Fibrosis—Scalene Biopsy—Bronchoscopy						
1	Pre-Anesthesia	80.0	79.0	—	34.6	7.45	44
2	Incision	67.5	69.0	—	37.2	7.43	45
3	10 min.	92.0	91.5	—	56.5	7.30	44
4	10 min.	99.0	98.0	100	72.5	7.18	44
5	10 min.	95.5	94.5	100	116.5	7.03	43
6	Incision closed	99.0	98.0	98.8	107.0	7.00	44
7	Bronchial lavage	86.5	85.5	85.5	79.5	7.12	44
8	100% oxygen	99.0	99	98.5	72.8	7.12	46
9	Room air	74.5	74.5	70.25	57.2	7.20	43

patient. The gross appearance of the patient's blood in artificial light may be misleading. In general, the laboratory results of Beckman or Van Slyke techniques arrive too late to monitor the patient safely during bypass. Our reflection oximeter provides a reading which is immediately available to the cardiac surgeon. Adjustments of flow, catheter positions, speed of disc rotation, temperature and so forth, may be made at once, if indicated, to safeguard the patient. In our present technique a line is run from the arterial line distal to the arterial filter of the heart-lung machine. Blood is thus propelled by the arterial pump through the oximeter cuvette and then returns to the collecting

chamber on the venous side of the heart-lung machine. A second such line is run in similar fashion from the venous line or one may draw a venous sample from the bottom of the venous reservoir if desired.

The data obtained on four representative clinical cases are shown in Tables III-VI to illustrate the usefulness of this reflection oximeter and to compare it with the Beckman and Van Slyke determinations.

TABLE V.

SAMPLE	SOURCE	% SAT. BECKMAN	% SAT. VAN SLYKE	% SAT. R. O.	pH	pCO_2 (mm. Hg)	Hct.
	Case 3. D. P.—14 years—Atrial Septal Defect—Pump Oxygenator						
1	Artery	95.5	—	96.0	7.58	16.2	37
2	Vein	76.5	—	77.0	7.51	21.3	37
3	Pump	62.0	63.0	59.5	7.23	50.5	42
4	Artery	91.5	93.75	91.5	7.53	18.1	34
5	Vein	95.25		96.0	7.54		38
6	Vein	76.0		74.0			
7	Artery	96.5		96.0	7.35		40
8	Pump	96.5		96.0			
9	Pump	97.0		97.0			42
11	Vein	89.0	87.5	89.0	7.34		39
17	Artery	94.5		94.5	7.35		41
19	Vein	74.0		72.7	7.24		41
20	Vein	68.5		68.5	7.26		41
21	Artery	96.5		96.5	7.38	24.5	41
23	Artery	98.0		98.5	7.30		40
24	Artery			98.0	7.37	32.3	39
25	Artery			98.0	7.40	33.0	

TABLE VI.

TIME	LOCATION	Hgb.	OXYGEN CONTENT	OXYGEN CAPACITY	% SAT. BECKMAN	% SAT. R. O.	% SAT. VAN SLYKE
	Case 4. R. S.—17 Years—Ventricular Septal Defect						
3:08	RPA	14.1	14.43	19.10	76.5	74.0	75.0
3:08	BA	14.1	18.25	19.10	95.5	95.0	96.5
3:15	PA	14.1	15.00	19.10	78.5	77.75	76.25
3:15	BA	14.1		19.10	97.0	96.5	96.75
3:29	RPA	14.2	15.40	19.10	80.5	79.0	78.75
3:31	MPA	—	14.20	19.10	78.0	—	—
3:32	HVR_1	—	14.70	19.10	77.0	76.7	—
3:32	HVR_2	—	14.50	19.10	76.0	77.35	—
3:34	HVR_3	—	14.00	19.10	73.25	74.8	—
3:35	MRV	14.1	14.20	19.10	74.25	75.25	71.5
3:36	RV/TV	—	14.50	19.10	76.0	74.75	—
3:37	L-IVC	14.1	13.40	19.10	70.0	70.1	—
3:38	H-IVC	—	13.85	19.10	72.5	72.12	71.25
3:45	L-RA	—	15.30	19.10	80.0	78.12	—
3:46	M-RA	—	14.50	19.10	76.0	75.0	—
3:47	H-RA	14.1	15.00	19.10	78.5	77.0	76.75
3:47	RA/VC	—	15.30	19.10	80.0	81.5	—
3:49	SVC	—	15.16	19.10	79.25	79.8	—

SUMMARY

1. A new reflection oximeter is presented utilizing two wave lengths (805 mμ and 650 mμ) and heparinized whole blood.

2. The oxygen saturation values are absolute and independent of temperature, and hemodilution, as well as cell size, shape, and origin.

3. There is no significant difference in the standard deviation between Van Slyke, Beckman, and reflection oximeter determinations of oxygen saturation.

4. This reflection oximeter is practical and useful clinically.

The authors gratefully acknowledge the administrative and technical assistance of Mother Mary Loreto, S.P., Sister Mary Clare, S.P., and Sister Mary Aloysia, S.P., St. Vincent Hospital, Worcester, Mass.

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(For Discussion, see page 637.)

THE REPAIR OF CIRCUMFERENTIAL DEFECTS OF THE TRACHEA BY DIRECT ANASTOMOSIS: EXPERIMENTAL EVALUATION

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DESPITE the persistent efforts of numerous investigators, the continuing need for an adequate tracheal substitute has not been answered. The various prosthetic materials, which have yielded good results in other areas, have not proved satisfactory for this purpose. Homologous and heterologous tracheal grafts have invariably resulted in stenosis and failure. A variety of other methods has been equally unsatisfactory.

In our own laboratory, repeated efforts to develop such a substitute have met with consistent failure. In marked contrast to these discouraging experiences were the highly satisfactory results of end-to-end anastomosis of the trachea in certain related experiments. This observation suggested the importance of determining the limits of feasibility of primary anastomosis in the repair of circumferential defects. The experiments described in this report were designed to determine those limits in terms of a parameter which might allow transfer of the experimental results to clinical practice.

METHODS

Adult mongrel dogs, weighing from 8 to 25 kilograms, were anesthetized with sodium pentobarbital and were allowed to breathe spontaneously without the use of an endotracheal tube. The cervical trachea was exposed through a longitudinal midline incision extending from the lower end of the thyroid cartilage to the sternal notch. The cervical region was chosen because of the ease of approach and anesthetic management and the lack of complicating factors in the postoperative recovery. The trachea was first mobilized from the cricoid cartilage to the sternal notch; all blood vessels entering this segment of trachea were divided and ligated. The mediastinal trachea was then mobilized by finger dissection to the level of the main bronchi so that the entire trachea lay free of attachment from the cricoid to the carina. Circumferential resection of varying amounts of trachea was then performed. A spring balance calibrated in grams was attached to each end of the divided trachea and the tension required to approximate the divided ends was measured. All measurements were made with the animal's head flexed to a position of 90 degrees with respect to the vertebral column. End-to-end anastomosis was then carried out using interrupted 4-0 braided stainless steel sutures. The anastomosis was tested for air leaks and

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the wound irrigated with 200 ml. of a 1 per cent solution of Neomycin. The wounds were closed without drainage. Each animal received 1,000,000 units of penicillin and 0.5 Gm. of streptomycin immediately after operation. No effort was made to maintain immobility of the head and neck in the postoperative period.

Those animals which died during the postoperative period were subjected to autopsy to determine the fate of the anastomosis and the cause of death. Those which survived were sacrificed at intervals from 2 weeks to 6 months. The state of the anastomosis was noted with particular reference to the presence or absence of stenosis, the preservation of the supporting cartilages, the number of cartilages remaining, and the integrity of the mucosal lining. The condition of the distal tracheobronchial tree and lung was studied with respect to the presence of infection, consolidation, or other pathologic condition.

RESULTS

It was recognized at the inception of these experiments that significant differences exist between the trachea of dog and man and that the results would not be directly transferable to the human in terms of length of segment or number of rings resected. It appeared possible, however, that a correlation between suture-line tension and successful primary healing might be more significant in this regard.

The initial experiments were designed, therefore, to establish the relationship between the length of trachea resected and the tension required for approximation. Preliminary studies revealed that the degree of tension was directly dependent upon the extent to which the trachea was mobilized. Investigation was therefore undertaken to determine whether or not such mobilization would impair the circulation of the organ so seriously as to preclude primary anastomosis. It was found that division of all vessels entering the trachea from the cricoid to the bifurcation impaired neither the viability nor the healing ability of the organ. Injection studies which were performed to clarify this problem demonstrated extensive collateral vascular channels (Fig. 1).

In light of these results, the trachea was completely mobilized in all subsequent experiments. Under these conditions, it was found that the curve relating the length of trachea resected to the tension required for approximation assumed an exponential form, increasing increments of tension being required with resection of each succeeding ring (Fig. 2). Flexion of the head to 90 degrees with respect to the vertebral column reduced the tension significantly below the values obtained in extension.

Experiments were then undertaken to determine the maximal tension compatible with routine primary healing of the anastomosis. Utilizing the technique noted above, 42 animals were subjected to resection of varying lengths of trachea with primary anastomosis of the remaining segments. Of these, 2 failed to recover from anesthesia, one died at 2 days of unexplained cause but with an intact anastomosis, and 3 were not subjected to autopsy. These 6 animals were excluded from the group of definitive experiments.

In the definitive group of 36 animals, the average number of tracheal rings was found to be 39.7, with upper limits of 44 and lower limits of 34 rings. The defects created in this group ranged from 8 to 27 rings. The results of these

experiments are shown in Table I. It will be noted that all anastomoses performed at a tension less than 1,700 grams proved successful. At values greater than 1,700 grams, the results became unpredictable, but it is interesting to note that a number of anastomoses healed satisfactorily at significantly higher levels of tension. The animals may be divided into 3 categories: (1) those in which primary healing resulted, (2) a single animal in which partial disruption occurred, and (3) those in which complete disruption resulted.

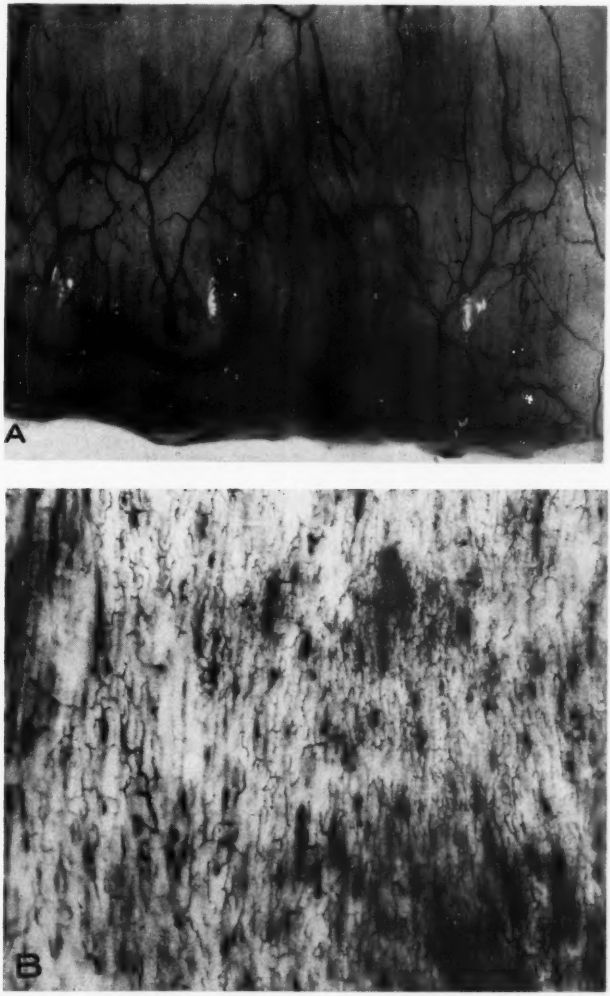

Fig. 1.—*A*, Enlarged view of the external aspect of the canine trachea following injection of the thyroid artery. The extensive collateral communication between the segmental arteries is clearly demonstrated.

B, Enlarged view of the mucosal aspect of the canine trachea following injection of the arterial system. The submucosal vascular plexus is demonstrated.

1. Primary healing resulted in 21 animals in which the percentage of the tracheal rings resected varied between 20 and 58 per cent. Suture-line tension ranged from 400 to 2,750 grams and the defects created varied from 5 to 15 cm. in length. These animals spontaneously limited the degree of extension of the neck for several days following operation, but by the end of 7 days most animals could accomplish full extension of the neck. Laryngeal function, as manifested by the ability to bark, was not altered. No airway problems were encountered. Autopsy revealed minimal fibrous tissue reaction about the trachea (Fig. 3).

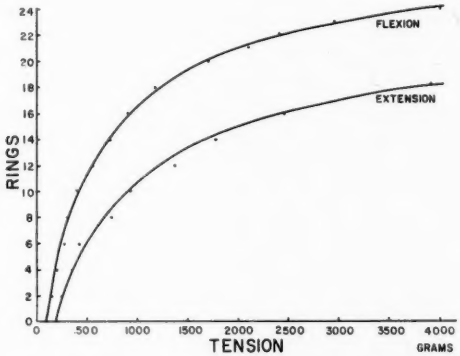

Fig. 2.—The relationship between the tension required for approximation and the number of rings resected. The marked effect of flexion of the head upon suture-line tension is illustrated.

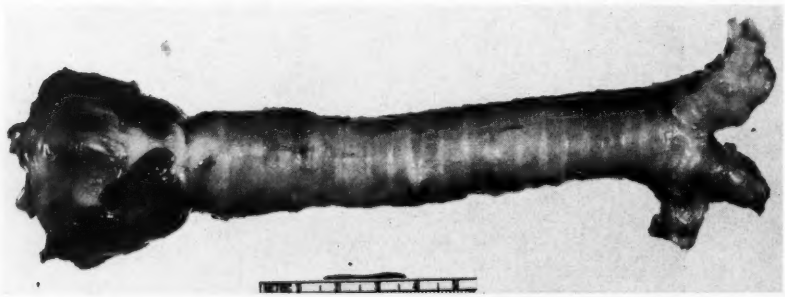

Fig 3.—Autopsy specimen of the trachea from an animal which had been subjected to resection of 19 rings with successful primary anastomosis at a tension of 2,750 grams. Twenty rings are present in the remaining trachea.

TABLE I. TRACHEAL RESECTION AND PRIMARY ANASTOMOSIS

ANASTOMOTIC TENSION (GM.)	NO. RINGS RESECTED	NUMBER OF ANIMALS	HEALED/ DISRUPTED	% PRIMARY HEALING
400-1,199	8-21	7	7/0	100
1,200-1,499	18-24	4	4/0	100
1,500-1,699	17-23	6	6/0	100
1,700-1,899	17-25	7	2/5	29
1,900-2,099	22-23	3	0/3	0
2,100-2,299	22-26	5	2/3	40
2,300-3,100	19-27	4	1/3	25

No distortion of the larynx or mediastinal structures was apparent but the distance between the tracheal cartilages was significantly increased. The diameter of the trachea appeared grossly normal. In all animals in this group, the mucosa was intact as were the cartilages. The intraluminal portion of the sutures was covered by mucosa (Fig. 4) except in those animals sacrificed shortly after operation. Stenosis at the suture line was negligible and even the most marked stenosis noted was not functionally significant. No instances of bronchial or pulmonary infection were noted. On microscopic examination (Fig. 5), scarring was

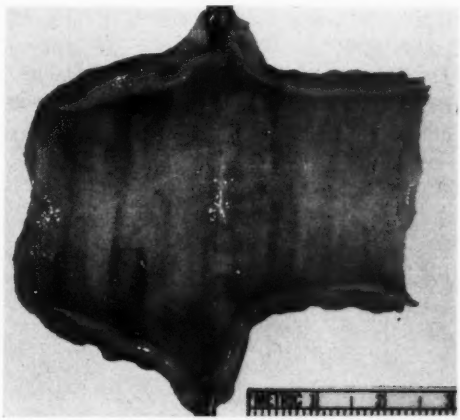

Fig. 4.—Mucosal aspect of the anastomotic line from the trachea shown in Fig. 3. The suture line is cleanly healed with virtually no stenosis. The sutures and suture line are covered by epithelium. The cartilages are intact.

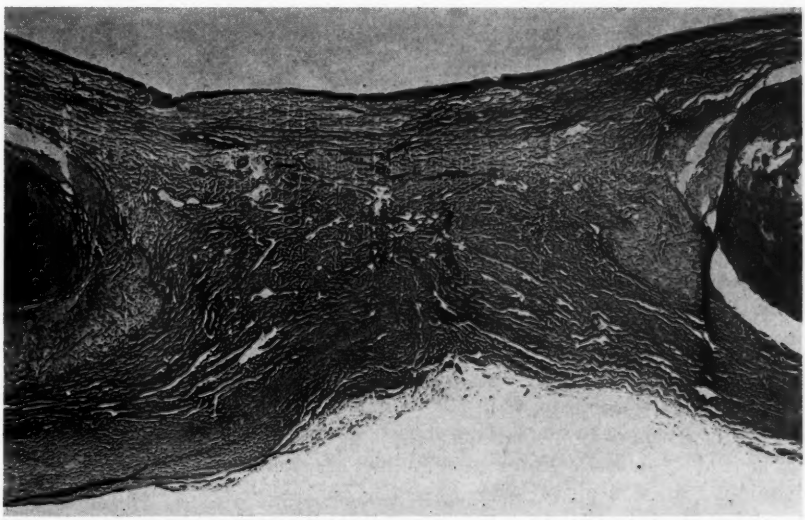

Fig. 5.—Photomicrograph of suture line which shows minimal scarring and intact ciliated epithelium across suture line. (× 15; reduced ¼.)

minimal and normal ciliated respiratory epithelium covered the suture line. The adjacent cartilages appeared normal as did the intercartilaginous membrane.

2. One animal in which the suture-line tension was 1,825 grams was sacrificed at 2 weeks. The animal appeared clinically well but was found to have a 3 mm. disruption involving approximately 25 per cent of the suture line. Loss of both the cartilaginous rings and mucosa was noted in this area. The remainder of the anastomosis was well healed. There was minimal stenosis at the time of sacrifice.

3. Disruption of the anastomosis occurred in 14 animals in which the percentage of tracheal rings resected varied from 46 to 63 per cent and suture-line tension varied between 1,700 and 3,100 grams. If separation of the tracheal segments occurred within 48 hours, the animals demonstrated severe airway obstruction and mediastinitis. Disruption occurring after 48 hours was not accompanied by mediastinitis, air leak, or immediate airway obstruction but was

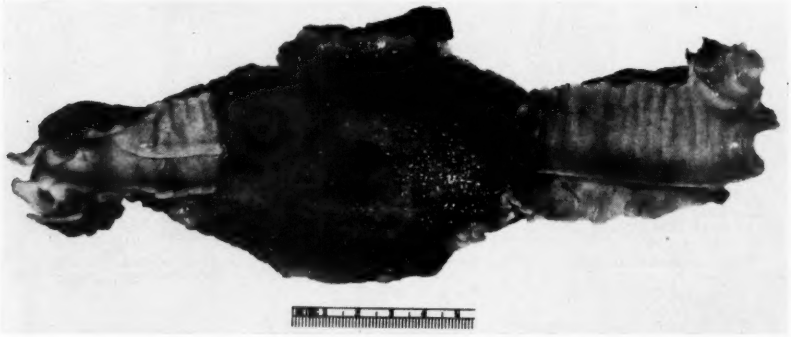

Fig. 6.—Autopsy specimen of disrupted suture line showing separation of tracheal segments and a 9 cm. granulation-lined sinus tract. Twenty-two rings had been resected and anastomosis performed at a tension of 1,825 grams. Eighteen rings are present in the remaining trachea.

marked by the development of an inspiratory stridor which became progressively more severe until the dog was sacrificed. In all animals of this group, autopsy revealed complete separation of the suture line, the sutures usually being retained in the upper tracheal segment. The distal trachea retracted deep into the mediastinum and the defect between the proximal and distal ends was occupied by a sinus tract lined with granulation tissue and walled off from the cervical and mediastinal tissues by a fibrous tissue capsule (Fig. 6). This sinus tract was invariably grossly infected and an associated purulent bronchitis and pneumonitis was usually present.

DISCUSSION

Although non-circumferential defects of the trachea may be repaired by a variety of techniques, the reconstruction of circumferential losses poses an infinitely more difficult problem. Several possible approaches may be considered.

Homografts.—The use of homografts or heterografts is not currently available because of our inability to circumvent the immune response of the host. It

seems unlikely that this technique will provide entirely satisfactory results even though the problem of immune rejection of foreign tissue be resolved. Consistently successful transplantation of such an extensive composite graft cannot be expected despite the work of Correll and Beattie[2] which suggested that free autogenous transplants of this type can survive. There would appear to be no satisfactory manner of providing such a graft with an immediate blood supply by vascular anastomosis.

Prostheses.—On the basis of technical considerations alone, substitution of an inert prosthesis for the resected segment would seem to be the simplest means of restoration of continuity. To date, however, no satisfactory permanent prosthesis has been devised. If this technique is to be successful, the prosthesis must reproduce with a reasonable degree of accuracy certain characteristics of the organ. It must provide support adequate to maintain the patency of the airway during inspiration yet must be sufficiently flexible to accommodate to the movement of the trachea associated with motion of the head and neck, respiration, and deglutition. It is unfortunate that a degree of rigidity sufficient to provide the required support often results in erosion of the supporting cartilages of the trachea adjacent to the defect. The prosthesis must also provide an immediate, intact epithelial lining, since a barrier must be established between the infected tracheal lumen and the adjacent tissues if success is to be achieved. Failure to provide such a lining results in the formation of an infected sinus tract across which the tracheal epithelium will not proliferate. Obstruction of the lumen by granulation tissue is the inevitable result. These considerations place an additional demand on the supporting element in that it must be porous enough to allow penetration of stromal elements adequate to nourish an epithelial graft.

The paradoxical nature of these requirements is apparent and the problem of devising a prosthesis which satisfies these conditions is obviously complex. Nonetheless, for the repair of very extensive tracheal defects, the development of a composite prosthesis which meets these requirements seems to offer the best chance of success.

Autogenous Tissue.—A substitute trachea constructed from autogenous tissue would seem to provide a possible approach. Such tissue might be either local or distant in origin but must still conform to the requisite characteristics noted above. While local tissue is available in the cervical region, it is virtually nonexistent in the mediastinum and in neither region does the available tissue possess the required characteristics. The problems associated with bringing distant tissue with these characteristics to the various regions of the trachea are exceedingly difficult and time consuming. Although the use of intercostal muscle to repair partial defects of the intrathoracic trachea has proved satisfactory, experimental evaluation of this technique in our laboratory did not indicate any potential value of the technique for circumferential defects.

Primary Anastomosis.—It has been known since the late years of the nineteenth century that end-to-end anastomosis could be accomplished with excellent results in small defects of the trachea. It has generally been accepted, however,

that the applicability of this method is quite limited. The basis for this restriction has been the supposedly inviolate segmental blood supply, which precluded mobilization, and a low intrinsic elasticity which negated its value.

Two critical fallacies are present in this line of reasoning. Although the blood supply of the trachea is, indeed, segmental, the factor which has not been generally recognized is the presence of an extensive collateral vascular plexus. This plexus provides an entirely adequate circulation even after total ligation of the segmental vessels and mobilization of the trachea. A source of arterial inflow and venous outflow must presumably be left at each end of the trachea. In the procedure utilized in our experiments the only vascular supply remaining was that provided by the superior thyroid vessels above and the vessels entering below the tracheal bifurcation.

The concept of limited elasticity is not borne out by our investigations. The trachea is a remarkably flexible and elastic structure designed to provide mobility while maintaining adequate support of the airway. This dual role is accomplished by separation of the relatively rigid cartilaginous rings by the strong intercartilaginous membranes which are composed chiefly of collagen. These membranes are ideally adapted to respond to tension, either acute or chronic.

Experimental evaluation of end-to-end anastomosis in the dog has been reported by Maisel and Dingwall[5] and by Ferguson and his co-workers.[3] The latter investigators attempted to correlate the length of trachea resected with tracheal elasticity and suture-line tension. In their series, however, the longest segment resected measured 6 cm. and the greatest tension to which the technique was subjected was 1,000 grams, the average tension being 285 grams. The limitation of tension to these low figures was based on their experimental observation that the majority of the increase in length available with increased tension is obtained at a tension of approximately 450 grams. Our data fail to confirm this limitation. It should also be noted that the measurements given by Ferguson and his associates were made with the head in full extension. Measurements made under these circumstances yield a figure for maximum tension to which an anastomosis may be subjected but give an entirely erroneous impression of the normal stress. The anastomoses in the present series, however, were constantly subjected to a tension equal to or greater than the measured tension. While the work of these investigators clearly revealed the feasibility of primary anastomosis in the repair of tracheal defects, it did not extend the method to the limit of its capacity.

Kiriluk and Merendino[4] reported the results of resection of short segments of the intrathoracic trachea in 4 animals, all of which developed significant degrees of stenosis secondary to separation of the suture line. Suture-line tension was not measured and the factors which resulted in separation cannot be ascertained but may in part be related to failure to mobilize the trachea.

Sonn and Klein[6] have reported encouraging results in the resection of from 9 to 13 rings in dogs. Mobilization of the trachea was not carried out, but the authors attributed their satisfactory results to the technique of making relaxing incisions in the intercartilaginous membranes of the remaining trachea. In a

series of experiments not herein reported, this technique was evaluated and found to add little to the available length of the trachea if adequate mobilization of the trachea had been previously carried out. Furthermore, the procedure was accompanied by significant hazard. Our studies would indicate that this technique is, in fact, strongly contraindicated.

Numerous clinical reports have clearly demonstrated the healing capacity of the tracheobronchial tree and interest has recently been renewed in the repair of tracheobronchial defects by direct anastomosis. Barclay, McSwan, and Welsh[1] have reported 2 cases in which resection of the carina has been carried out with primary reconstruction. The defects measured 5 cm. in length. They, too, emphasize the value of mobilization in obtaining sufficient length for anastomosis.

The available evidence suggests, therefore, that this method is feasible in the repair of much larger defects than has been generally accepted. It should again be emphasized that the results of our experiments cannot be transferred directly to the human being in terms of number of rings resected or length of defect. Furthermore, it must be realized that the length of defect which can be closed by this technique will vary with the age of the patient, the presence of inflammatory reaction or fibrosis of the trachea, and any other factors which affect the ability of the trachea to stretch in response to tension. Although impossible to determine with certainty, we believe that the variability in our results at high degrees of tension is in all probability due to variation in the age of the animals. In a series of human tracheas obtained at autopsy, we have found that in persons over 80 years of age the resection of more than two rings results in a degree of tension which exceeds the limits permissible in the experimental animal.

The correlation between successful primary healing and suture-line tension appears to be valid in the experimental animal but the ability to transfer these results to the human remains uncertain. In view of the basic similarity in structure of the trachea in dog and human, it would not seem unreasonable to suggest that the limits of tension under which canine and human trachea may be successfully anastomosed may also be similar. The results of these experiments may at least provide a first approximation of the limits of feasibility of primary anastomosis in the human being.

CONCLUSIONS

1. In the experimental animal, primary anastomosis has yielded excellent results in the repair of circumferential defects of the trachea if excessive suture-line tension is avoided.

2. The limits of feasibility of this technique are much greater than has been previously recognized. The success or failure of primary anastomosis can be predicted on the basis of the tension under which the anastomosis is performed.

3. Suture-line tension may represent a parameter which will allow transfer of these results from the experimental animal to clinical practice. In the dog,

anastomoses performed under a tension of less than 1,700 grams invariably resulted in primary healing. Those performed at a tension between 1,700 and 2,200 grams yielded unpredictable results. In those anastomoses performed at a tension greater than 2,200 grams, success was rarely achieved.

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(For Discussion, see page 637.)

PULMONARY ARTERIAL BLOOD FLOW THROUGH AN ACUTELY ATELECTATIC LUNG

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WHEN performing an operation within the thorax it is impossible to avoid some compression of the lung. The fraction of the pulmonary arterial blood which perfuses the compressed portion of the lung constitutes a right-to-left shunt of venous blood to the systemic arteries. The magnitude of the shunt will depend upon the rate of blood flow through the atelectatic lung. It has long been known that when a lung has been collapsed for weeks or months the blood flow through it is greatly diminished. Under these circumstances, the flow is less than 10 per cent of its former value.[3] There is no unanimity of opinion, however, as to when and how rapidly the flow decreases after the lung is collapsed. This question is of some interest to thoracic surgeons. If the blood flow through pulmonary tissue compressed by a retractor or a pack immediately and markedly decreases, the shunt will be small and there may be little if any fall in the saturation of systemic arterial blood with oxygen, especially if the lungs are being ventilated with that gas. On the other hand, if the blood flow through the compressed lung remains unchanged, or increases, and if the uncollapsed pulmonary tissue is not being ventilated with an oxygen enriched gas mixture, the saturation of arterial blood with oxygen will fall. The degree of unsaturation will be more profound, the greater the amount of lung which is collapsed. To study this problem the following experiments on an acutely atelectatic lung were performed in 35 dogs with the thorax open.

METHODS AND MATERIALS

The square-wave electromagnetic flowmeter, developed by Denison, Spencer, and Greene,[5] was used to measure the blood flow through the main and the right and left pulmonary arteries before and after inducing complete collapse of the left lung. An electromagnetic probe with a circumference approximately 80 per cent of that of the vessel was used for the blood flow measurements. Using a probe slightly smaller than

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the artery results in a constant cross-sectional area at the point where blood flow is measured. Spencer and Denison[12] have pointed out that this amount of constriction does not decrease the flow through the vessel. Electromagnetic probes with an internal circumference of either 25 or 30 mm. were found to be the appropriate sizes for the pulmonary arteries in which the flow was measured. These probes and the flowmeter were calibrated by pumping blood at predetermined rates through excised canine arteries of the same circumference as those encountered in the experimental animals. The voltage induced in the blood stream was picked up by the probe, amplified by the flowmeter, and recorded by a Sanborn-150 direct writing recorder. After calibration, a nomogram was constructed which correlated the deflection produced by the flowmeter with known flow rates. In our hands, the accuracy of the method was ±8 per cent (range of one standard error of estimate). Before each experiment, the sensitivity of the flowmeter was adjusted so as to obtain a standard deflection from a known external voltage.

The oxygen saturation of blood was measured by a cuvette oximeter which had been calibrated by direct determinations of the oxygen saturation of blood by the method of Van Slyke and Neill.[14] The cuvette oximeter was connected through a three-way stopcock to a polyethylene catheter in the femoral artery. The third limb of the stopcock led to a transducer which had been calibrated previously with a mercury manometer. The blood pressure was thus continuously measured and the oxygen saturation of the arterial blood was intermittently determined by turning the stopcock and drawing blood through the cuvette.

Procedure.—The dogs were anesthetized with pentobarbital sodium. The initial dose was 30 mg. per kilogram of body weight supplemented by 2.5 mg. per kilogram of body weight each hour in order to maintain a steady anesthetized state. A mechanical respirator was used to ventilate the lungs with oxygen through a non-rebreathing system. The respiratory rate was 16 per minute with an inflating pressure of 20 cm. of water.

In 12 dogs the thorax was entered through the left fourth intercostal space and the pulmonary artery and bronchus supplying the left lung were isolated. One of the probes was placed around the left pulmonary artery which was then temporarily occluded with a cotton tape just distal to the probe. The deflection observed on the recorder, with the artery occluded, represented the base line or zero flow. After the lungs had been ventilated with oxygen for one hour, the left pulmonary arterial blood flow, the saturation of systemic arterial blood with oxygen, and the systemic blood pressure were measured. The probe was then removed from around the pulmonary artery, the lung manually collapsed and the left main-stem bronchus ligated with a broad cotton tape. Occluding the bronchus with a metal clamp was found to produce an erroneous recording of blood flow because the metal produced an alteration in the electromagnetic field. The probe was replaced and the same measurements made ½ hour after the lung was collapsed and at hourly intervals for 3 hours. The ligature occluding the bronchus was then cut and the lung re-expanded. The measurements were repeated 15 minutes and one hour after re-expansion of the lung. Six animals were used for control experiments.

A. In one dog, the effect of anesthesia, thoracotomy, and isolation of the left pulmonary artery and the left bronchus on pulmonary blood flow through the left lung was measured for 3 hours.

B. In one dog the effect of collapse of the left lung on cardiac output was observed. In this animal the same operative procedure was followed except that the main pulmonary artery was also isolated and was used for measurement of cardiac output.

C. In 4 dogs a median sternotomy was performed, both right and left pulmonary arteries and the left bronchus were isolated, and the left lung was collapsed as previously described. Blood flow was measured through both the right and left pulmonary arteries.

The results of the other 17 experiments had to be discarded; in 7 instances, because worms *(Dirofilaria immitis)* were present in the heart and pulmonary arteries at autopsy, and, in 10 instances, because of shock upon induction of anesthesia, cardiac arrhythmia, or hemorrhage.

RESULTS

Pulmonary blood flow through an atelectatic left lung was measured in 16 dogs; 4 of these also served as control experiments (C). In all animals, immediately after collapse of the left lung, there was an increase in the depth and rate of respiration, an increase in the pulse rate, and a rise in systemic blood pressure. Within a half hour, these parameters had returned to their former values. The pulmonary arterial blood flow through the atelectatic lung was unpredictable for about 45 minutes after bronchial ligation. In 7 of 16 animals, after ½ hour the flow was significantly greater than before collapse of the left lung. In 5 dogs the flow was significantly decreased and

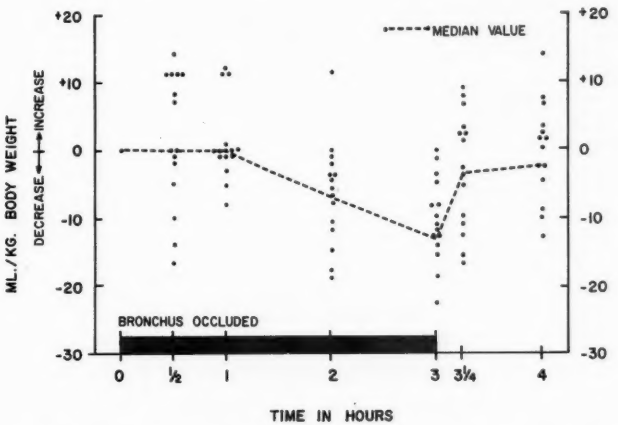

Fig. 1.—Graph which illustrates the changes in left pulmonary arterial blood flow before and after collapse of the left lung in 15 of 16 cases. The results in Experiment 5 are not included on the graph but can be found in Table I.

in 4 it was virtually unchanged. One hour after bronchial ligation, the median value of the pulmonary arterial blood flow through the atelectatic lung was not significantly different from the preligation value ($P > 0.05$) (Fig. 1, Table I). At this time, the median value of the oxygen saturation of the peripheral arterial blood had fallen to 88 per cent (Fig. 2). During the remaining 2 hours of atelectasis, pulmonary arterial blood flow through the left lung gradually diminished so that at the end of 3 hours the median value was significantly below normal ($P < 0.01$). Concurrently, the median value for the saturation of systemic arterial blood with oxygen had gradually increased to 94.5 per cent.

Fifteen minutes after the bronchial ligature was cut and the lung re-expanded, pulmonary blood flow had risen significantly in 12 of 16 animals. In all but one case (No. 3), the oxygen saturation of the systemic arterial blood had returned to normal (Table I, Fig. 2). One hour after reinflation of the lung, the median pulmonary arterial blood flow did not differ significantly from the control value ($P > 0.05$). In all animals, the oxygen saturation of the systemic arterial blood had returned to normal.

TABLE I. BLOOD FLOW THROUGH LEFT PULMONARY ARTERY AND SATURATION OF SYSTEMIC ARTERIAL BLOOD WITH OXYGEN BEFORE, DURING, AND AFTER ATELECTASIS OF LEFT LUNG

EXPER. NO.	DOG WEIGHT (KG.)	PROBE SIZE (MM.)	CONTROL BLOOD FLOW (ML./MIN.)	TIME INTERVALS AFTER COLLAPSE OF LEFT LUNG								TIME INTERVALS AFTER REINFLATION OF LEFT LUNG			
				½ HR.		1 HR.		2 HR.		3 HR.		¼ HR.		1 HR.	
				BLOOD FLOW	O_2 SAT.	BLOOD FLOW	O_2 SAT.	BLOOD FLOW	O_2 SAT.	BLOOD FLOW	O_2 SAT.	BLOOD FLOW	O_2 SAT.	BLOOD FLOW	O_2 SAT.
1	18	30	850	660	87	820	82	630	79	760	79	870	97	—	—
3	19.5	30	930	1,160	57	930	58	560	68	480	79	600	92	740	96
4	18	30	740	930	90	930	84	660	90	550	94	500	100	710	100
5	25.5	30	1,640	760	95	600	95	400	98	190	98	490	100	1,040	100
9	20	30	820	820	95	820	90	710	92	580	94	600	97	550	100
10	15	30	390	510	92	390	96	330	99	150	99	330	100	420	100
11	14	30	480	420	95	480	91	390	93	280	85	330	100	360	100
12	15.5	30	560	730	63	540	77	450	91	360	97	310	99	360	100
13	20	30	760	620	93	700	77	590	94	590	94	640	99	650	100
15	14	30	450	550	93	450	96	420	95	390	97	480	100	510	100
21	22.5	25	710	1,040	66	990	84	710	90	550	95	870	100	870	100
23	15.5	25	530	690	65	690	67	690	73	530	79	480	100	500	100
28	19	25	450	420	86	430	89	440	88	250	95	520	99	510	100
32	17	25	310	220	93	220	95	90	98	80	98	450	100	540	100
33	26	30	870	820	88	660	90	450	94	360	96	1,100	100	1,100	100
35	16	30	450	450	85	470	87	300	88	410	87	480	100	480	100

TABLE II. BLOOD FLOW THROUGH RIGHT AND LEFT PULMONARY ARTERIES BEFORE, DURING, AND AFTER ATELECTASIS OF LEFT LUNG

EXPER. NO.	DOG WEIGHT (KG.)	PULMONARY BLOOD FLOW (ML./MIN.)																					
		CONTROL			½ HR.			1 HR.			2 HR.			3 HR.			3 HR., 15 MIN.			4 HR.			
		RT.	LT.	TOTAL	RT.	LT.	TOTAL	RT.	LT.	TOTAL	RT.	LT.	TOTAL	RT.	LT.	TOTAL	RT.	LT.	TOTAL	RT.	LT.	TOTAL	
20(B)	24.5			1,490			1,640			1,560			1,380			1,560			1,640			1,560	
28(C)	19	760	450	1,210	920	420	1,340	1,070	430	1,500	1,010	440	1,450	1,010	250	1,260	930	520	1,450	980	510	1,530	
32(C)	17	760	310	1,070	840	220	1,060	960	220	1,180	900	90	990	920	80	1,000	870	450	1,320	580	540	1,120	
33(C)	26	1,400	870	2,270	1,900	820	2,720	2,030	660	2,690	2,030	450	2,480	2,160	355	2,515	1,160	1,100	2,260	1,160	1,100	2,260	
35(C)	16	600	450	1,050	760	450	1,210	870	470	1,340	690	300	990	710	410	1,120	680	480	1,160	650	480	1,130	

In the control experiment (A), in which the left pulmonary arterial blood flow was measured every 30 minutes for 3 hours while the lung was being normally ventilated, no significant change in flow rate occurred. The six determinations of blood flow were 820, 760, 820, 870, 820, and 740 ml. per minute.

In the control experiment (B), blood flow through the main pulmonary artery was measured for one hour before, for 3 hours after producing atelectasis of the left lung, and at 15 minutes and one hour after release of the bronchial ligature and reinflation of the lung. No significant progressive change in cardiac output was observed (Table II).

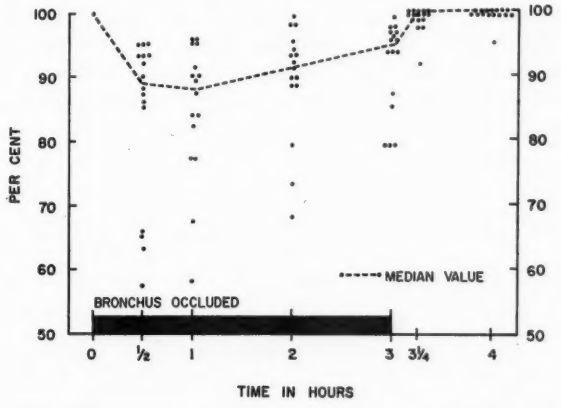

Fig. 2.—Graph which illustrates the changes observed in saturation of the systemic arterial blood with oxygen before and after acute collapse of left lung.

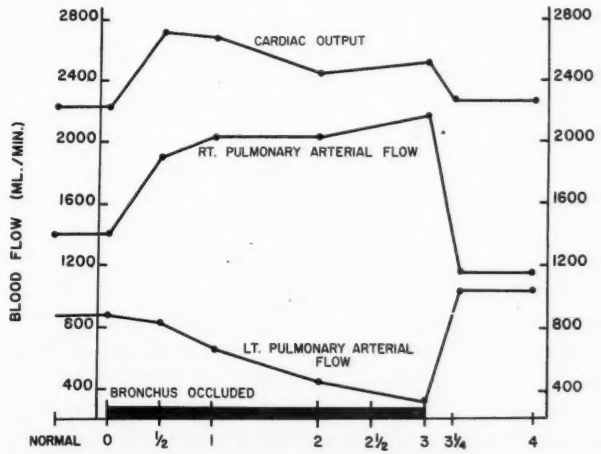

Fig. 3.—Control experiment (33C). The blood flow through the right and left pulmonary arteries is shown. The change in cardiac output does not parallel the change in blood flow through the collapsed left lung.

In the four control experiments (C), the blood flow through both the left and the right pulmonary arteries was measured. An increase or decrease in blood flow through one pulmonary artery was generally reflected by a reciprocal change in the other pulmonary artery (Fig. 3, Table II). Cardiac output was obtained by adding the two rates of flow. The variations in cardiac output did not parallel the changes in blood flow through the collapsed lung. In all of these dogs, the cardiac output increased immediately after left bronchial occlusion; in 2 it remained elevated for the duration of the experiment.

A statistical analysis of the relationships between left pulmonary arterial blood flow and left lung weight, total lung weight or body weight revealed that a significant correlation existed only between left pulmonary arterial blood flow and body weight. For this reason, in Fig. 1, changes in left pulmonary arterial blood flow were expressed in terms of milliliter per kilogram of body weight per minute. Thus changes in blood flow in this figure are comparable regardless of the size of the dog.

DISCUSSION

Moore[10] in 1931 published an excellent review of previous studies of blood flow through atelectatic lung. Some authors reported that the blood flow through a lung immediately after its collapse was normal.[4, 7, 8] Others reported that it was markedly decreased.[1, 2, 9, 10] In all these reports the flow of blood through the atelectatic lung was measured indirectly. In a number of reports unwarranted assumptions were made: namely, that the blood flows through the right and left lungs of dogs were equal,[2] or that the cardiac output remained unchanged, or, if changed, that it could be estimated by assuming a constant stroke volume with a varying pulse rate.[10]

A number of reports[1, 7, 8, 9] estimate the blood flow through an atelectatic lung from the degree of unsaturation of the systemic arterial blood with oxygen. Frequently the authors did not indicate that the ventilatory rate and minute volume were kept constant, nor did they indicate the composition of the ventilatory gas.

In some of the earlier work, atelectasis was presumed to have been produced by occluding a bronchus with a balloon at the end of a catheter. However, at autopsy the lungs were found to be normally inflated.[7, 8]

A steady cardiorespiratory state is necessary in order to compare blood flow measurements made at different times. Immediately after total collapse of the left lung, the systemic blood pressure and pulse rate rose, and spontaneous, heaving, deep respiratory movements occurred. These phenomena persisted for 30 to 45 minutes. The blood flow through the atelectatic lung during this period was variable. Lack of consideration of this fact may explain the variations in previous estimates of pulmonary blood flow through an acutely collapsed lung.

There may be two possible causes for the gradual decrease in pulmonary blood flow through the collapsed left lung; either the cardiac output gradually

diminishes after the atelectasis has been produced or local changes occur within the atelectatic left lung which increase the resistance to blood flow. Since we observed no decrease in cardiac output after collapse of the left lung in five experiments, it seems likely that vascular resistance increases in the collapsed lung. The mechanism for, and the site of, this increased vascular resistance is not apparent and merits further study.

The rise in pulmonary arterial blood flow toward the control value, after release of bronchial obstruction and reinflation of the lung, indicates that after 3 hours of complete atelectasis the changes in the collapsed lung are reversible. Apparently, in prolonged atelectasis the diminished pulmonary arterial blood flow becomes permanent.[3]

The cardiac output in the 5 dogs, in which it was measured, averaged 71 ml. per kilogram of body weight. This is a somewhat lower figure than those obtained by other methods of determining cardiac output in dogs with closed chests.[6, 13] The lower cardiac output we observed may have been the result of an opened thorax and general anesthesia.[11]

During a thoracic operation the diminution in the oxygen content of systemic arterial blood when the lung is compressed may be harmful. Patients may develop cardiac arrhythmias, hypotension, or even cardiac arrest. This is particularly true in patients with coronary atherosclerosis. Occlusion of the pulmonary artery supplying the compressed lung, or reinflation of the collapsed lung, will restore the normal systemic arterial oxygen saturation.

SUMMARY

1. Acute atelectasis was produced in the left lung of 16 dogs by manual compression followed by bronchial occlusion.

2. One hour after collapse of the left lung, the flow of blood through the left pulmonary artery was not significantly changed. During the subsequent 2 hours the blood flow gradually decreased.

3. The oxygen saturation of the systemic arterial blood tended to vary inversely as the blood flow through the collapsed lung.

4. In five experiments the cardiac output, during 3 hours of collapse of the left lung, did not parallel the diminution in blood flow through the left pulmonary artery.

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(For Discussion, see page 637.)

THE EFFECTS OF POSITIVE PRESSURE LUNG INFLATION UPON PULMONARY VASCULAR DYNAMICS

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THE EFFECTS of positive pressure ventilation upon pulmonary vascular dynamics should be clearly understood whenever manual and mechanical methods of augmenting respiration are employed. Although the changes resulting from positive pressure lung inflation have been studied extensively, there has been sufficient variation in experimental techniques and interpretation of results for the problem to be still surrounded by considerable controversy.[1-4]

The present experiments concern the effects of static levels of positive airway pressure upon the pulmonary vascular dynamics of the excised lungs of the dog. The results of this study indicate that there is a direct relationship between the level of airway pressure and the size of the pulmonary vascular bed. In addition, it appears that in response to positive pressure lung inflation, the pulmonary vessels behave differently in the open chest than in the closed chest. No inference, however, can be drawn from this work as to the effects of positive pressure lung inflation upon related factors operating in the intact animal, such as venous return, cardiac function, or systemic blood flow.

METHODS

A. *Equipment and Procedure.*—Freshly excised lungs from 10 dogs were used in these experiments. The heart, lungs, and trachea were removed from the animal en bloc and supported in the vertical position (Fig. 1). The trachea was connected to a source of compressed air, with a manometer attached to the line. Two catheters were passed through the wall of the right ventricle into the main pulmonary artery and positioned so that their tips lay just beyond the pulmonic valve. The larger catheter was attached to a fluid injector by which the pulmonary vessels were perfused. The pressure within the main pulmonary artery was monitored via a Statham P23D strain gauge attached to the second catheter. The drainage from the lungs was collected by means of a large tube in the left atrium and subsequently measured.

The injector consisted of a steel chamber containing saline solution under pressure of 150 pounds per square inch. With this high pressure the outflow was constant and

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could be considered independent of back pressure. The flow from the injector was governed by an electronically controlled solenoid valve, which opened and closed intermittently at a predetermined rate, so that the pulmonary vessels were perfused in a pulsatile manner. When the valve opened a constant flow rate was achieved almost instantaneously. This flow continued at a uniform rate for the duration of the injection (one second in these experiments) and was then as rapidly shut off by closure of the valve. The result was a series of fluid injections, each of known and constant volume, which entered the main pulmonary artery in the form of a "square wave." With this method of perfusion, based upon a technique described by Peterson,[5] the variable volume and complex form of the cardiac ejection is replaced by a controlled volume injection of simple and predetermined shape.

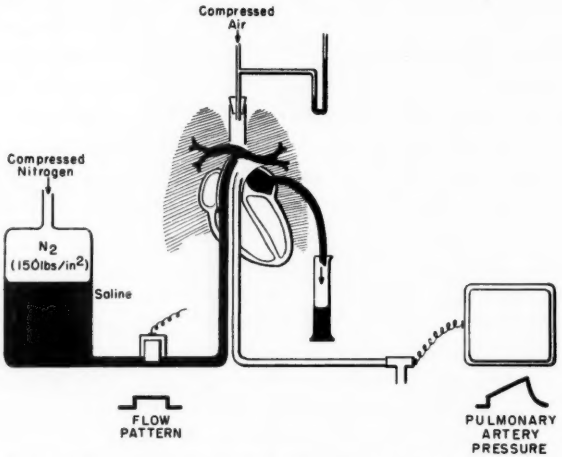

Fig. 1.—Schematic representation of the experimental set-up. The flow pattern of the injection ("square wave") is shown on the *left* and the form of the resulting pressure curve within the pulmonary artery is indicated on the *right*.

Initially, the lungs were completely collapsed. They were then progressively inflated with air via the trachea in stepwise pressure increments equivalent to 5 cm. H_2O, from zero up to 30 cm. H_2O, and allowed to deflate in similar steps. Each specimen was carried through three complete cycles of inflation and deflation. At every pressure increment and decrement, several injections, each consisting of 30 ml. saline in the form of a "square wave," were made into the main pulmonary artery.

B. *Analysis and Interpretation.*—From the pattern of the pressure curves measured in the main pulmonary artery during each injection, certain changes in the characteristics of the pulmonary vascular bed were determined. Since the volume and pattern of the injections remained constant, variations in the form of the resulting intravascular pressure curves were determined primarily by the characteristics of the vascular bed. Therefore, these pressure curves lend themselves to the following analysis and interpretation.

Fig. 2 is a recording of the typical pressure pattern obtained within the main pulmonary artery during the course of an injection. The record shows an initial, brief, steep pressure rise (*a* to *b*) which then, abruptly, gives way to a more gradually rising slope that continues throughout the duration of the injection (*b* to *c*). The downward excursion at the start of the record is an artifact due to the jet of the injection, and the final portion represents the run-off.

The duration of the first upward slope is so short that very little fluid enters the pulmonary vessels during this period. The level to which the pressure rises during this

portion of the curve is interpreted as indicating the pressure which must be reached within the main pulmonary artery before flow through the vessels of the lung can actually begin. This is the pressure level which is necessary to open the pulmonary vessels to accommodate the flow and to accelerate the fluid in the vascular bed. It will be referred to as the "perfusing pressure." The subsequent, less steeply rising slope (*b* to *c*) shows the increase in intravascular pressure associated with the gain in fluid within the pulmonary vessels as the rapid inflow during the injection temporarily exceeds the outflow. This portion of the record reflects the pressure necessary to distend the vascular bed to accommodate the net gain in fluid volume. It is thus an index of the "volume-distensibility" characteristic called "compliance."

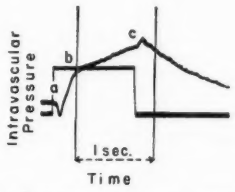

Fig. 2.—Sample record of the pressure changes occurring within the main pulmonary artery during the course of injecting 30 ml. of saline solution in the form of a "square wave." There is, at first, a sharp pressure rise (*a* to *b*) which is followed by a more gradual increase in pressure (*b* to *c*) that continues through the course of the injection. The second line represents the electrical signal which indicates by the sudden up-sweep that the solenoid valve is opened, then remains open during the period indicated by the elevated horizontal trace, and closes again at the sharp down stroke.

RESULTS

The results reported here show the changes in "compliance" and "perfusing pressure" of the pulmonary vascular bed which occur with variations in endotracheal pressure in the isolated, excised lungs of the dog. The data are summarized on Table I and Fig. 3. "Compliance" is reported as the percentile change from the values obtained at the start of each experiment when the lungs were completely collapsed. Since it is proportional to the reciprocal of the pressure rise, an increase in "compliance" indicates that the same fluid volume can be accommodated in the pulmonary vascular bed with a smaller rise in intravascular pressure. The "perfusing pressure" is expressed directly in millimeters of mercury.

The findings indicate that when the completely collapsed lung is inflated by progressively increasing endotracheal pressure, there is, at first, an increase in vascular "compliance" and a decrease in "perfusing pressure." Thus, less pressure is required to distend and perfuse the pulmonary vessels for the same volume flow. However, when the airway pressure rises to the range of 15 to 20 cm. H_2O (the pressure at which the lung first appears to be fully expanded), then any further increase in airway pressure causes a decrease in "compliance" and increase in "perfusing pressure." As the lung is then allowed to deflate, but short of complete collapse, there is a continuous and marked increase in "compliance" and decrease in "perfusing pressure."

The second inflation cycle, which refers to the now expanded lung, yields curves which are significantly different from those obtained with the collapsed lung. When raising the airway pressure in the expanded lung there is a

TABLE I. CHANGES IN PULMONARY VASCULAR "COMPLIANCE" AND PULMONARY "PERFUSING PRESSURE" DURING THREE CONSECUTIVE CYCLES OF INFLATION AND DEFLATION OF THE EXCISED LUNGS*

	AIRWAY PRESSURE (CM. H_2O)												
	0	5	10	15	20	25	30	25	20	15	10	5	0
First Inflation Cycle													
Pulmonary vascular "compliance" (% change from collapsed state)	100%	155%	200%	251%	252%	184%	142%	154%	194%	254%	332%	400%	
Pulmonary "perfusing pressure" (mm.Hg)	14.5	9.8	8.6	7.0	6.8	7.5	9.0	6.8	3.6	1.6	0.4	0.3	
Second Inflation Cycle													
Pulmonary vascular "compliance" (% change from collapsed state)	520%	440%	360%	290%	230%	168%	146%	166%	205%	260%	320%	410%	
Pulmonary "perfusing pressure" (mm.Hg)	0.3	0.8	1.7	2.5	4.1	6.2	8.1	6.2	4.5	2.5	1.0	0.7	
Third Inflation Cycle													
Pulmonary vascular "compliance" (% change from collapsed state)	510%	395%	336%	264%	198%	158%	138%	160%	210%	285%	350%	430%	518%
Pulmonary "perfusing pressure" (mm.Hg)	0.6	0.8	1.9	3.3	4.5	6.0	8.5	6.0	5.3	3.5	1.7	0.8	0.4

*The figures are the mean values obtained at these levels of airway pressure in ten separate experiments.

continuous decline in "compliance" and rise in "perfusing pressure" throughout the entire range of increasing pressure. Both these curves are then similarly reversed when the lung is permitted to deflate. A subsequent inflation and deflation gives essentially the same curve as that obtained with the second cycle.

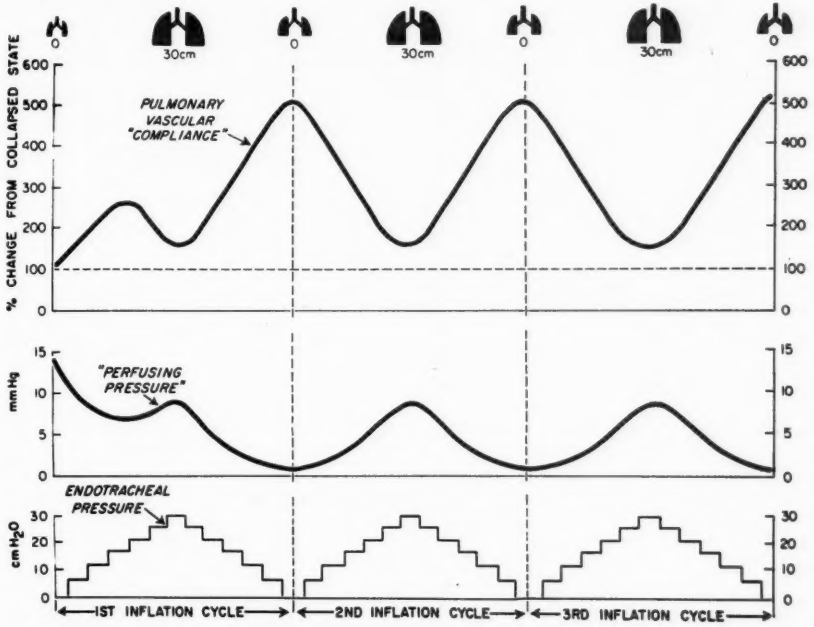

Fig. 3.—Changes in pulmonary vascular "compliance" and "perfusing pressure" during three successive cycles of positive pressure inflation and deflation of the excised lungs. Initially, the lungs were completely collapsed. At the beginning of the second and third cycles the lungs were expanded.

DISCUSSION

The results of this study can be summarized thus: With the initial inflation of the collapsed lung, "compliance" at first increases and "perfusing pressure" declines. This continues until all portions of the lung are expanded. Any additional increase in airway pressure then results in a decrease in "compliance" and an increase in "perfusing pressure." When applying positive airway pressure to an expanded lung, any increase in the pressure above the ambient level leads to a decrease in "compliance" and increase in "perfusing pressure" which is reversed as the airway pressure is reduced.*

The explanation for these findings may be as follows. In the collapsed lung, the smaller vessels also collapse and their walls are in apposition.

*The observation that flow through the vessels of the expanded lung will continue despite the fact that the "perfusing pressure" is less than the endotracheal pressure may be attributed to the pressure drop between the alveoli and the blood vessels as a result of the elastic deformation of the walls of these structures.

Thus, because surface tension forces have to be overcome, more pressure is necessary to distend and perfuse these vessels than would be required to achieve the same flow through open vessels. As the lung is progressively inflated, the expanding parenchyma exerts traction upon the blood vessel walls which tends to open the vessels and facilitate pulmonary flow. However, raising the endotracheal pressure above the level needed to keep the lungs expanded leads to compression of the smaller, thin-walled pulmonary vessels as a result of overexpansion of the airways. This again reduces the size of the functioning pulmonary vascular bed so that a higher intravascular pressure is needed to obtain the same volume flow. As the airway pressure is then reduced, but short of complete lung collapse, the vessels can re-expand and the vascular pressure will decline.*

The observed variations in the "volume-distensibility" characteristic ("compliance") also can be attributed to changes in the size of the pulmonary vascular bed. The relationship between the size of the vascular bed and its coefficient of "volume-distensibility" (D) is defined as the ratio of the fractional change in volume (dV/Vo) to the change in pressure (dP), where: dV = net increase in intravascular volume during the injection, dP = the corresponding rise in the intravascular pressure, and Vo = the size of the vascular bed at the beginning of the injection.[6] Thus, $D = \frac{dV}{dP \cdot Vo}$, and it becomes apparent that when the injected volume (dV) remains constant, *and the volume of the vascular bed (Vo) has been diminished,* the rate of rise of the intravascular pressure during the injection (dP) will be increased, even though there has not been any actual change in the true tissue distensibility (D). Therefore, the *apparent* decrease in "compliance" with the increasing levels of airway pressure can be attributed to reduction in the size of the vascular bed, and does not necessarily imply any changes in the actual elastic properties of the walls of the blood vessels.

The results of these experiments, performed under *dynamic* conditions with pulsatile flow, are in agreement with the recent work of Permutt, Howell, Proctor, and Riley[6, 7] who studied the effects of lung inflation upon the static pressure volume characteristics of the pulmonary vessels, and Burton[4] who investigated the effects of lung inflation upon the pulmonary vascular resistance. The results reported here, as well as those of the above-named workers, indicate that the size of the pulmonary vascular bed is reduced both by complete lung collapse and by higher levels of airway pressures. These findings may help to clarify the controversy between those who suggest that positive pressure lung inflation leads to a *decrease* in the

*This relationship between airway pressure and blood vessel size may be made clear when expressed in terms of "transmural pressure" (TMP), as suggested by Burton.[4] TMP is the difference, for any blood vessel, between the intravascular pressure (P) and the surrounding tissue pressure (T), so that TMP = P – T. It is the transmural pressure, acting against the tension in the blood vessel wall, that determines the size of each distensible vessel. Thus, if the tension in the wall remains unchanged, any increase in the surrounding tissue pressure (T), as would occur with excessive inflation of the airways, will decrease the transmural pressure (TMP) and result in a reduction in the diameter of the vessels, and vice versa.

size of the pulmonary vascular bed[8, 9, 10] and those whose findings indicate an *increase.*[11] Thus, it appears that with lung inflation by positive airway pressure, progressing from complete lung collapse to inflation with pressure in excess of that required to keep the lung expanded, there is, initially, an increase in the size of the vascular bed as a result of traction upon the vessel walls. This increase is followed by reduction in the size of the vascular bed owing to compression of the smaller pulmonary vessels by the overexpanded airways. Therefore, *the size of the pulmonary vascular bed varies both with the level of airway pressure and the degree of lung inflation, with the maximum size for any given flow rate occurring at the lowest level of airway pressure compatible with inflation of the entire lung.*

The significant clinical application of these findings relates to the conditions which would be optimal for pulmonary blood flow when using positive pressure ventilation techniques. In the lung that can go to complete collapse, as in the open chest, this would be at the minimal airway pressure which would keep the lungs expanded. Under these circumstances, intermittent pressure peaks no higher than 15 cm. H_2O should be employed. Excessive airway pressure may be detrimental because of compression of the smaller pulmonary vessels, which, in a patient with a failing circulation, may so interfere with pulmonary blood flow as to lead to death. On the other hand, when ventilating an expanded lung, as in the case of assisted respiration with the chest intact, all positive airway pressures above the ambient level will tend to reduce the size of the vascular bed. Therefore, under these circumstances the lowest pressure compatible with an adequate volume of pulmonary ventilation should be employed.

SUMMARY

1. The effects of positive pressure lung inflation upon the pulmonary vascular dynamics of the excised dogs' lung has been investigated by artificially perfusing the pulmonary vessels in a pulsatile manner with controlled, constant volume saline injections. The resulting intravascular pressure pulses were analyzed in terms of (a) the pressure needed to open the pulmonary vessels and initiate flow (pulmonary vascular "perfusing pressure"), and (b) the pressure required to distend the pulmonary vascular bed during each pulsatile ejection (pulmonary vascular "compliance").

2. The results indicate that: (a) with progressive inflation of the initially collapsed lung there is, at first, a decrease in the "perfusing pressure" and an increase in "compliance" of the pulmonary vascular bed until the airway pressure reaches approximately 15 cm. H_2O. Airway pressures above this level lead to a reversal of both these factors. (b) In an expanded lung, the "perfusing pressure" is increased and the "compliance" is reduced in direct proportion to the increase in airway pressure throughout the entire range of pressure changes. Both factors are similarly reversed as the endotracheal pressure is reduced.

3. These findings indicate that, in the expanded lung, all levels of positive airway pressure above the ambient level lead to reduction in the size of the pulmonary vascular bed. In the collapsed lung, however, the vascular bed, at first, enlarges with positive airway pressure until the lung is expanded. Raising the airway pressure much above this level will then again reduce the size of the vascular bed as a result of compression of the smaller pulmonary vessels by the overexpanded airways.

4. The clinical significance of these findings relates to defining the ideal conditions for positive pressure ventilation techniques. Thus, it appears that if one is dealing with a lung which can collapse completely (as in the open chest), intermittent airway pressure up to 15 cm. H_2O will keep the lung expanded and maintain optimal conditions for pulmonary blood flow. However, in the expanded lung (as in the closed chest) any increase in airway pressure tends to interfere with pulmonary flow, so that under these conditions the lowest pressures compatible with an adequate volume of pulmonary ventilation should be employed.

The author wishes to thank Mr. James Papayoanou for the very capable technical assistance contributed throughout the course of this study.

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(For Discussion, see page 637.)

BRONCHOGENIC CARCINOMA PRODUCED EXPERIMENTALLY IN THE DOG

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MALIGNANT tumors are a major problem for the medical world, and bronchogenic carcinoma is the most important tumor. Bronchogenic carcinomas have been produced experimentally in small laboratory animals but bronchogenic carcinomas have not been readily produced in the dog which would be large enough for surgical study. This study reports success in producing carcinoma in the tracheobronchial tree of the dog.

Our interest in tracheal reconstruction led us to study the action and structure of the cilia in the tracheobronchial tree of dogs. We found that if a segment of cervical trachea were excised and re-implanted as a reversed autologous graft that for the first 4 days after implantation of the graft the ciliated columnar cells disappeared.[2] By the eighth postoperative day, cuboidal remnants of the respiratory epithelial lining was apparent in a significant portion of a surface area of the graft. By the eighteenth day, granulation tissue appeared below the cuboidal layer of cells which in turn were forming a second layer. After 23 days, the remnants of the trachea had good vascularity and was lined with ciliated columnar-type cells (respiratory epithelium). By the twenty-third day the cilia had regenerated. It was found that a drop of India ink placed on the re-implanted segment would be carried caudad by the cilia which continued to beat caudad. Thus cilia were demonstrated to retain the direction of their beat in a reversed autologous graft.

A further observation was made in these preparations.[3] It was found that the caudad anastomosis had cilia beating to it from both directions. In this situation a "mucous block" occurred and the cilia were luxuriant. This was in contrast to the more cephalad anastomosis where the cilia beat away from the anastomosis. Here the anastomosis was dry and squamous metaplasia occurred. The animals were followed for one to 2 years and it

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was found that the squamous metaplasia of the cephalad anastomosis and the "mucous block" of the caudad anastomosis were persistently unchanged for over 18 months.[4]

We then recognized that in one animal there was a preparation in which squamous metaplasia occurred, as well as a "mucous block."

The theories concerning the pathogenesis of bronchogenic carcinoma have indicated carcinogenic agents as etiologic factors. Cigarette smoking and the atmospheric environment are considered as possible carcinogens. Inhalation of carcinogens would take these particles with the inspired air toward the alveoli. It has been queried as to why bronchogenic carcinoma does not occur in the trachea if these carcinogens must pass through it. Hilding[6-9] has made an interesting speculation that the foreign material distally in the alveoli is carried through the action of the cilia toward the trachea and that, as the small bronchioles join to form larger bronchi, the concentration of carcinogens in the mucus increases. However, when the mucus, laden with particles, reaches the main-stem bronchi and the distal trachea, the normal cough reflex promptly expectorates the particle-laden mucus so that there is insufficient contact time for the irritant to act in the trachea. Thus, Hilding postulates that tumors occur where major "mucoid rivers" become confluent, but distal to the main-stem bronchus and trachea. A second speculation is that squamous metaplasia is a precursor of the bronchogenic carcinoma and that the carcinogen is more prone to produce tumor if a precursor of squamous metaplasia is already present. It is observed that the incidence of squamous metaplasia is higher in patients with bronchogenic carcinoma, but the exact etiologic role remains unclear.

Thus, there are three factors in the pathogenesis of bronchogenic carcinoma that seem worthy of consideration: (1) that carcinogen enters the lung, (2) that the mucous river concentrates the carcinogen at major bronchi, and (3) that squamous metaplasia may be a precursor of bronchogenic carcinoma. It became apparent to us that the preparation of the animal with the reversed trachea would possibly test these three factors since there was squamous metaplasia of the cephalad anastomosis, a "mucous block" in the trachea at the caudad anastomosis, and the animal could be exposed to known carcinogens in the more distal portion of the lung.

Kolb, Porta, and Shubik[10] reported in 1958 a technique of instilling benzanthracene distally into the bronchi of hamsters and produced tracheobronchial carcinomas. In 10 hamsters exposed to 50 μg of benzanthracene weekly for 44 weeks, 2 of 10 animals developed carcinoma of which one was in the trachea. Fifteen animals exposed to 50 μg weekly for 12 weeks developed no carcinomas. Sixteen animals exposed to 100 μg weekly for 17 to 20 weeks developed carcinoma in 7 of the 16 animals. Of these carcinomas, three occurred in the trachea and one in the main-stem bronchus. Accordingly, we decided to instill this same compound into dogs in which the cervical trachea had been reversed.

METHODS

In this series 24 dogs were operated upon under general anesthesia induced by pentobarbital. The trachea was exposed in the neck through a longitudinal incision and a segment of cervical trachea, four to eight cartilages in length, was reversed. In some animals this was done as a free graft, in others, both ends were severed and the segment was reversed without dividing the blood supply. Primary anastomoses were then carried out, employing interrupted silk sutures in most instances. Two animals were used as control animals; the other 22 animals were used as test animals. Of these 22 animals, 11 animals died, as summarized in Table I, from necrosis of the graft, stenosis of the graft, or infection. There were 11 animals that survived the reversal of the trachea in good condition. The interval after the trachea was reversed until the time the second part of the experiment began varied from one to 8 months and is also summarized in Table I.

TABLE I

DOGS	DATE OF OPERATION	DIED WITHOUT INJECTION	INTERVAL BEFORE TREATMENT (MO.)	TREATMENT PERIOD	TREATMENT (MO.)	INTERVAL—TREATMENT TO AUTOPSY
1	3/18/58		8	1/23/59-1/14/60	12	0
2*	3/18/58		8	1/23/59-2/24/60	13	0
3	3/6/58		8	1/23/59-9/8/59	8	0
4	3/25/58		4	1/23/59-7/31/59	7	0
5	10/28/58	11/9/58 Necrosis				
6	10/31/58	11/18/58 Necrosis				
7	11/6/58	Discarded				
8	11/18/58		2	1/23/59-4/17/60	15	0
9	12/2/58	Killed 2/11/59				
10	12/12/58	12/12/58				
11	12/18/58		1	1/23/59-7/24/59	7	0
12	12/23/58	1/13/59 Stenosis				
13	1/7/59		1	2/16/59-1/14/60	11	0
14	1/8/59		2½	3/26/59-4/23/60	13	8
15	1/19/59	2/12/59 Distemper				
16	1/26/59		2	3/26/59-4/14/60	9	0
17	2/12/59					
18	2/17/59		1	3/26/59-4/14/60	12	0
19	2/17/59	5/6/59 (?)				
20	3/5/59	3/26/59 Pneumonia				
21	3/13/59	5/6/59 Stenosis				
22	3/18/59		1	4/24/59-4/23/60	12	8
Control 1	7/8/59	---	-	0	--	17
Control 2	7/8/59	---	-	0	--	17

*Carcinoma.

The test animals received 9, 10, -dimethyl-1, 2, benzanthracene (DMBA).* This compound was prepared after the method of Kolb and his co-workers, by dissolving it in 3 to 5 c.c. of acetone added to 1 c.c. of 1 per cent gelatin in water at 56°C. in a water bath. The acetone was removed by bubbling nitrogen through the compound. The material was injected through the bronchoscope into the right main-stem bronchus of the dog as far into the lower lobe as possible. The animals were anesthetized with intravenous pentobarbital during each bronchoscopy. The dose of benzanthracene was

*Manufactured by Eastman Organic Chemicals, Rochester, N. Y.

arrived at experimentally. Table II illustrates the regimen employed in Dog 2. This was typical of the dosage. It will be noted that Dog 2 received 200 μg the first week and then 400 μg weekly for 3 weeks, followed by 1 mg. weekly for 18 weeks. The dose was increased to 5 mg. weekly for 14 weeks and then decreased to 1 mg. weekly for 19 weeks. The dog received 108.4 mg. of DMBA in the 13 month period.

TABLE II. DOSAGE OF DMBA IN DOG 2 WHICH DEVELOPED CARCINOMA

200 micrograms	× 1
400 micrograms	× 3
1 milligram	× 18
5 milligrams	× 14
1 milligram	× 19
Total: 108.4 milligrams	

The 11 animals treated with the DMBA died and were autopsied or were sacrificed at the conclusion of therapy as indicated in Table I. Two dogs, 14 and 22, were allowed to live for 8 additional months after cessation of treatment with DMBA before autopsy.

RESULTS

Microscopic sections were taken at autopsy through the caudad anastomosis, the distal trachea main-stem bronchi, and lungs, when indicated (Table III). Three animals had sufficient autolysis that no definite conclusions could be reached. All animals showed variations of squamous metaplasia. In 3 animals, invasive carcinomas were seen. Two of these occurred in the caudad anastomosis and one in the cephalad anastomosis. Fig. 2 shows the cephalad anastomosis of Dog 2 with squamous metaplasia. Figs. 3, 4, and 5 show invasive cancer in the caudad anastomosis of Dog 2. Fig. 6 is a photomicrograph of a polyp in the distal trachea of Dog 2.

TABLE III. MICROSCOPIC FINDINGS

DOG NUMBER	CEPHALAD ANASTOMOSIS	DISTAL ANASTOMOSIS	DISTAL TRACHEA	MAIN-STEM BRONCHUS	LUNG
1	Epithelium	Autolyzed	—	—	—
2	Ca-in-situ	Invasive Ca	P, SM	P, SM	P, SM
3	SM	SM	SM	SM	I
4	SM	SM	SM	P, SM	N
8	P, SM	P, SM	P	P	—
11	C	C	—	—	—
13	Epithelium	Autolyzed	SM	—	—
14	Ca-in-situ	Invasive Ca	P, ? Ca	Invasive Ca	—
16	Epithelium	Autolyzed	—	—	—
18	SM	SM	SM	SM	—
22	Invasive Ca	SM	P	P	I
Control 1	C	C	—	—	—
Control 2	C	C	—	—	—

Legend: C = Cilia. I = Inflammation. SM = Squamous metaplasia. P = Anaplasia papilloma. N = Normal.

SUMMARY AND CONCLUSIONS

1. Dimethylbenzanthracene was instilled into the trachea of dogs in which the trachea had previously been reversed. In 2 animals, invasive carcinoma

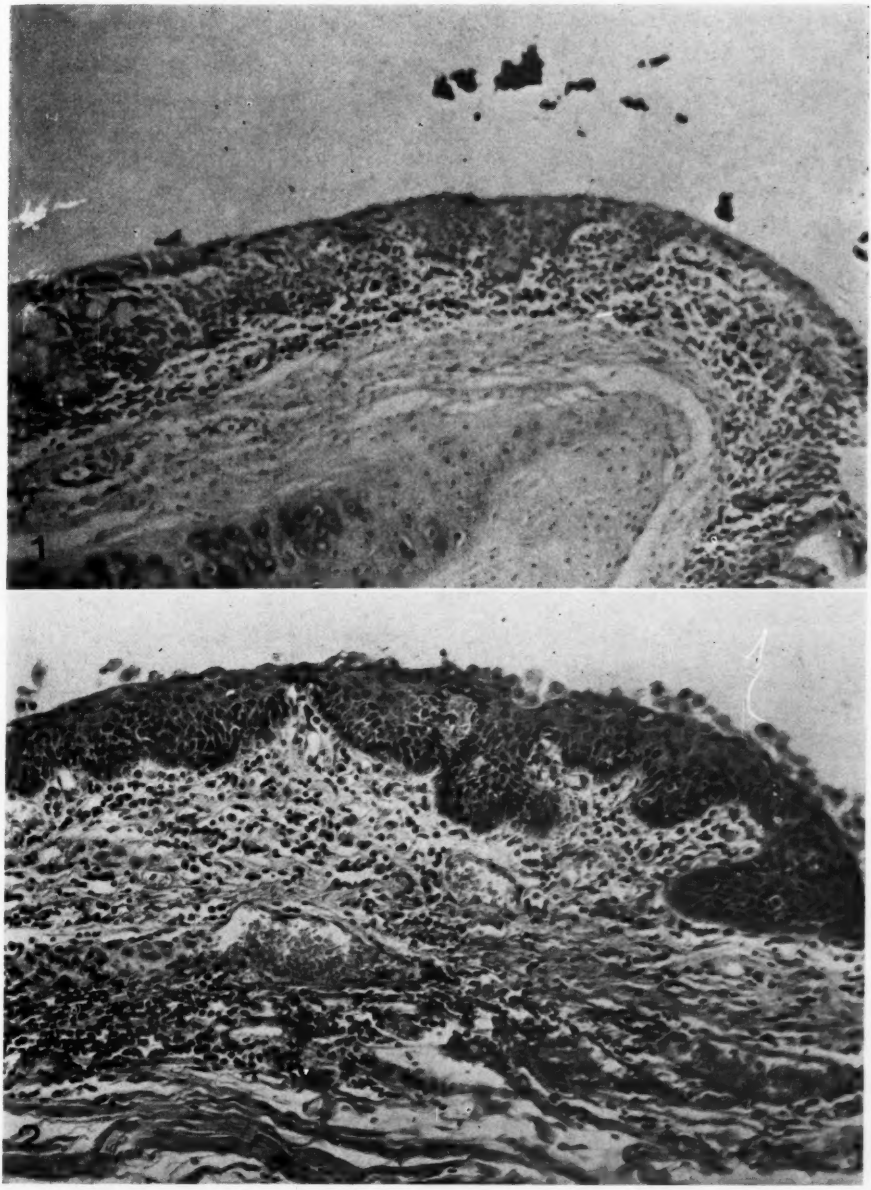
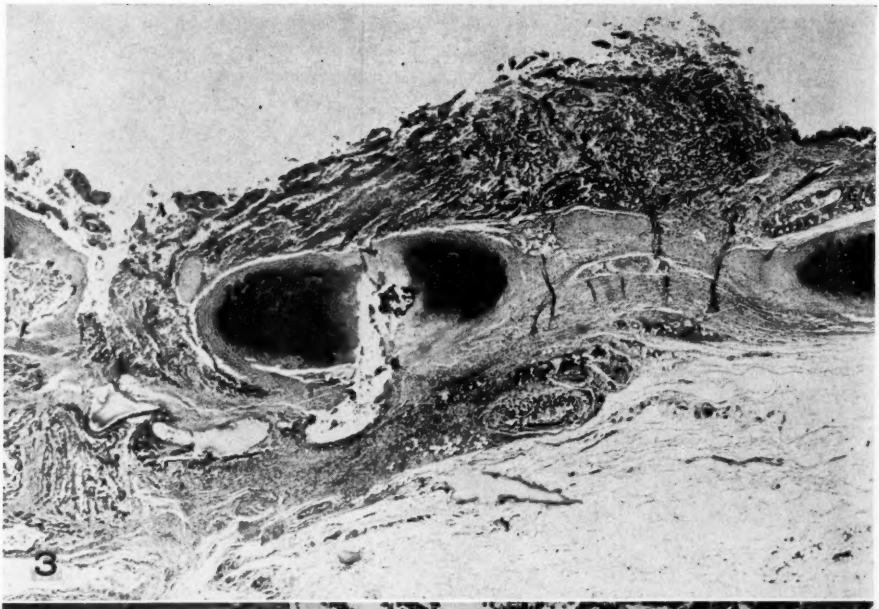


Fig. 1.—Cephalad anastomosis. Reversed cervical trachea in the dog showing squamous metaplasia.

Fig. 2.—Dog 2. Cephalad anastomosis showing carcinoma in situ. (×118; reduced ⅛.)



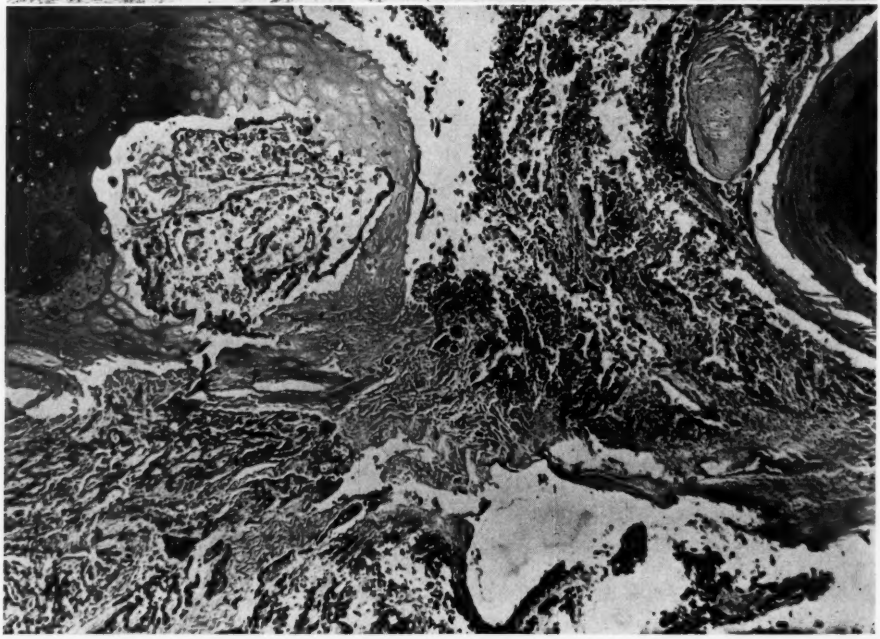
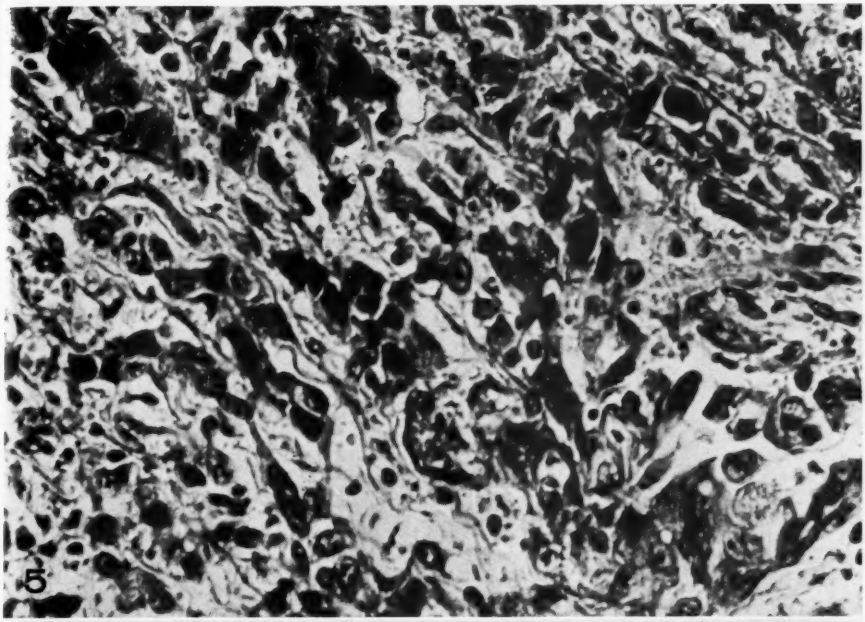


Fig. 3.—Dog 2. Caudad anastomosis showing carcinoma invading cartilage. (×18; reduced ⅙.)

Fig. 4.—Same as Fig. 3. (×35; reduced ⅙.)



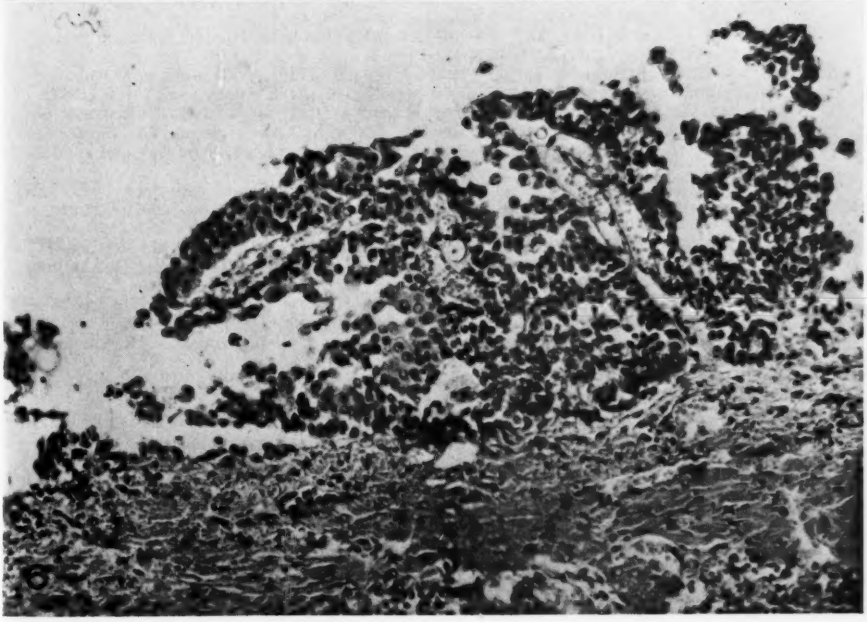


Fig. 5.—Same as Fig. 3. (×280; reduced ⅛.)

Fig. 6.—Dog 2. Distal trachea showing papilloma. (×118; reduced ⅛.)

was found in the distal cervical tracheal anastomosis. In one animal the carcinoma was in the proximal anastomosis. The tumor occurred in the animals in which therapy had been prolonged for 12 to 13 months. In 2 of these 3 animals the animal had been kept with no further therapy for 8 months before autopsy; the tumors had not spontaneously regressed.

2. It is possible that the "mucous block" in the distal cervical trachea increased the concentration of the carcinogen but this is not considered to be definitely established.

3. Additional work will be done to determine whether the normal dog will develop carcinomas of the tracheobronchial tree with instillation of dimethylbenzanthracene. If bronchogenic carcinoma can be produced regularly, this method should prove useful to study the production and treatment of lung tumors.

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(For Discussion, see page 637.)

HEMATOPORPHYRIN DERIVATIVE: A NEW AID FOR ENDOSCOPIC DETECTION OF MALIGNANT DISEASE

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HEMATOPORPHYRIN tends to accumulate in malignant tissue,[1, 2] and its accumulation and subsequent red fluorescence as a means of detection of cancer is not a new concept.[2-5] However, the materials and methods available in the past were both unrefined and unwieldy.[3-9] Consequently a more refined technique, based on the accumulation of an administered porphyrin in a tumor, was adopted, and extensive investigation was carried out to determine whether or not it could be used in the detection of cancer under certain circumstances.[10] We concluded[11] that malignant disease can be detected by utilizing an acetic acid-sulfuric acid derivative of hematoporphyrin and proper filter systems for activating and viewing the fluorescence. Thereupon we used the new technique in patients who were undergoing bronchoscopy or esophagoscopy or both for a known or suspected malignant lesion, and it is our experience with the use of fluorescent endoscopy that we wish to report.

EQUIPMENT AND PROCEDURES

A bronchoscopy or esophagoscope was specially modified so that it could illuminate a region with either a white light or the wave lengths (about 400 per millimicron) necessary for maximal activation of the hematoporphyrin derivative. A 200-watt high-pressure mercury lamp with a Schott filter provided light for activating the fluorescence (Fig. 1). This light was delivered from the lamp to the endoscope by means of a glass-fiber cable (Fig. 2).† When the light reached the endoscope it was transmitted down the scope by way of a transparent quartz rod of optical grade which replaced the usual light carrier (Fig. 3). The white light normally used for routine examination was provided by an otoscope bulb that fitted into the proximal end of the endoscope so that the light was transmitted by the same quartz rod. Thus, in order to change from the usual white light to the activating light, either the glass-fiber cable or the bulb was simply connected to the proximal end of the quartz rod.

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†Kindly provided through the courtesy of Dr. Walter P. Siegmund, American Optical Company, Southbridge, Mass.

Fig. 1.—Lamp house containing the mercury lamp together with stand and power supply used for endoscopic detection of malignant lesions.

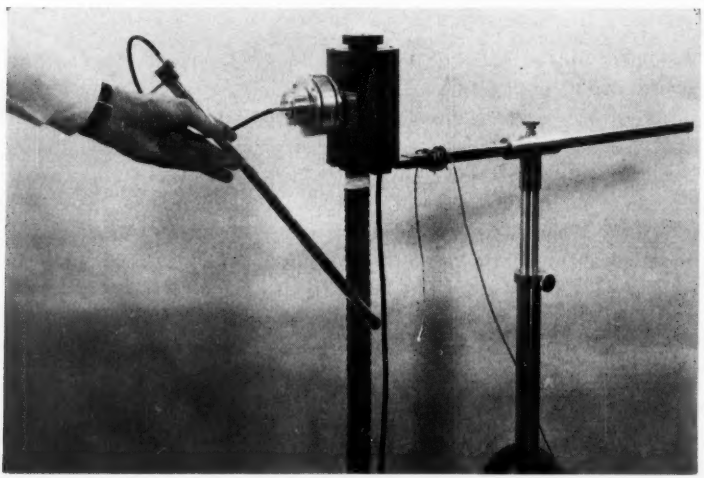

Fig. 2.—Bronchoscope attached to light source by flexible glass-fiber cable. White light is available by replacing the cable with an otoscope bulb.

A viewing filter which transmitted only the red light resulting from fluorescence was used by the operator while illuminating with the activating light. The viewing filter was in the form of glasses or an eye shield and was made from a Corning No. 3484 glass filter.

The hematoporphyrin derivative[10] was the acetic acid-sulfuric acid derivative of hematoporphyrin hydrochloride, which was prepared for intravenous administration in a concentration of 5 mg. per cubic centimeter and sterilized by filtration.*

The technique described was carried out on each of 15 patients known to have, or strongly suspected of having, a neoplasm of the esophagus or of the tracheobronchial tree so situated that the possibility of viewing it seemed good.

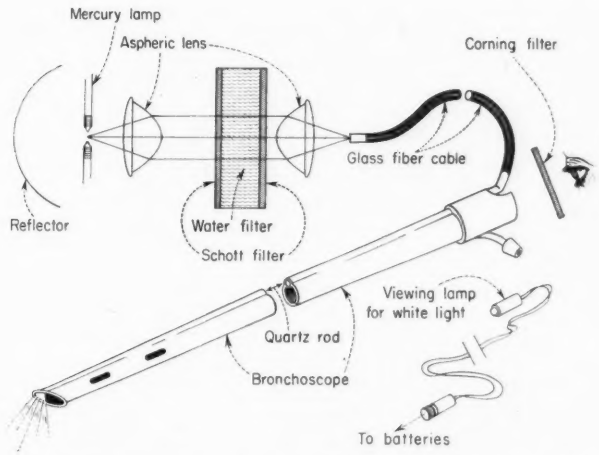

Fig. 3.—Manner of illuminating bronchoscope. Using a reflector, radius of curvature 38 mm., light from an OSRAM high-pressure mercury lamp, HBO 200 watt, is transmitted through a condensing system of two Pyrex aspheric lenses 35 mm. in diameter and having a focal length of 20 mm. Between the lenses is a 2-cm. water cell with two 3-mm. No. BG12 Schott filters. A glass-fiber cable, 18 inches long, conducts the blue-violet fluorescing light to the end of the quartz rod in the bronchoscope and the red fluorescence is examined through a Corning No. 3484 filter. To view with white light the cable is removed from the bronchoscope and replaced by the otoscope bulb.

Nine had bronchoscopy, 5 had esophagoscopy, and one had bronchoscopy and esophagoscopy. Each patient was given the hematoporphyrin derivative in a single intravenous injection of 2 mg. per kilogram of body weight approximately 3 hours before endoscopy. The derivative was injected into the rubber tubing used for the intravenous infusion of 5 per cent glucose in water because of the burning sensation produced by injecting it directly into the vein. After 3 to 4 hours the patient was prepared and examined in the usual manner. The bronchus or esophagus was first viewed with white light and then with the activating blue-violet light. Specimens of the lesions were removed for biopsy and sent to

*Now made available to us through the courtesy of Abbott Laboratories.

the pathologist as an unknown. After the procedure the patient was instructed to stay out of the direct sunlight for 36 hours because of the possibility of a transient photosensitivity caused by the porphyrin.[11]

RESULTS

The results of our studies in 15 patients are summarized in Table I. In every case in which a malignant lesion was located where the activating light would reach it in sufficient intensity, the region of malignant involvement exhibited a red fluorescence. Opposed to this was the grayish-white to black appearance of normal tissue as well as the black color of blood when examined with the activating light and viewing filter. Fluorescence was not influenced by the cell type of the malignant lesion.

TABLE I. CANCER DETECTION WITH HEMATOPORPHYRIN DERIVATIVE

CASE	SEX AND AGE (YEARS)	DIAGNOSIS	GRADE	SITE OF OBSERVATION	FLUORESCENCE
1	F 71	Squamous cell carcinoma	4	Mid-esophagus	Positive
2	M 52	Adenocarcinoma	4	Cardia	Positive
3	M 46	Adenocarcinoma	3	Hiatal hernia	Positive
4*	M 62	Recurrent adenocarcinoma	3	Esophagogastric junction	Negative
5*	M 53	Recurrent carcinoma	3	Esophagogastric junction	Negative
6	M 71	Squamous cell carcinoma	4	Mid-esophagus (esophagoscopy)	Positive
				Trachea (bronchoscopy)	Positive
7†	F 66	Metastatic carcinoma from breast (adenocarcinoma)	4	Right main bronchus (stenosis)	Positive
8	M 67	Small cell carcinoma	4	Left main bronchus	Positive
9	M 71	Metastatic carcinoma, pancreas (small cell)	4	Left main bronchus (no tumor)	Negative
10	M 55	Squamous cell carcinoma	3	Right main bronchus	Positive
11	M 48	Small cell carcinoma	4	Right lower lobe bronchus	Positive
12	M 64	Empyema	-	Right main bronchus (no tumor)	Negative
13	M 60	Carcinoma (squamous cell carcinoma)	4	Left main bronchus	Positive
14*	M 59	Metastatic pleural effusion (adenocarcinoma)	3	Right lower lobe bronchus (bronchial deformity)	Negative
15*	M 58	Carcinoma (squamous cell carcinoma)	4	Right lower lobe bronchus	Negative

*No tumor found on endoscopy.

†Photosensitivity was experienced by patient because of her negligence in following instructions.

As seen in Table I, there were no false-positive results. In 3 cases the malignant lesion was located so that the light did not reach it at all or reached it with insufficient intensity. In these cases, fluorescence was absent or was so slight that it could not be considered as diagnostic.

The only adverse side effect was a minor degree of photosensitivity exhibited by a patient (Case 7) who did not follow our instructions regarding immediate exposure to direct sunlight. The sensitivity to the sun lasted a few days and caused only slight discomfort to the patient.

REVIEW OF ILLUSTRATIVE CASES

In Case 1 a roentgenogram showed evidence of a constricting lesion of the lower part of the esophagus (Fig. 4). On esophagoscopic examination, a benign-appearing obstruction was demonstrated. However, this lesion exhibited red fluorescence when viewed with the activating light. Biopsy revealed a squamous cell epithelioma, grade 3, thus confirming the malignant nature of the lesion.

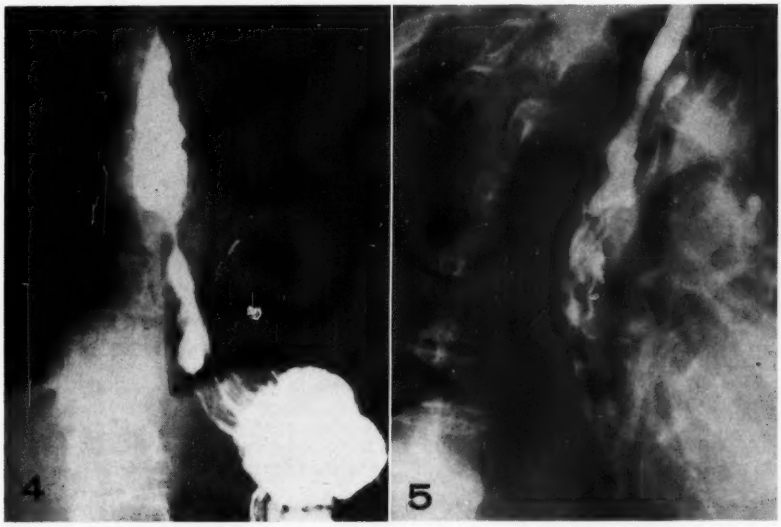

Fig. 4.—(Case 1). View of obstructing lesion in lower third of esophagus.
Fig. 5.—(Case 6). View of esophagus showing obstructing lesion in middle third of esophagus.

In Case 6 a roentgenogram showed evidence of an obstructing lesion in the middle third of the esophagus (Fig. 5). The region in question exhibited red fluorescence and biopsy proved the presence of a squamous cell epithelioma (grade 2). Next, the trachea was examined with a bronchoscope; a bulging deformity of the posterior tracheal wall was noted but without apparent invasion of the mucosa. When this region was viewed with the activating light, red fluorescence was noted through the tracheal mucosa. This case suggests that the technique may be helpful in the recognition of adjacent malignant lesions which have not penetrated through the mucosa.

One patient (Case 4) had had total gastrectomy for carcinoma of the stomach, and esophagojejunostomy had been done. A roentgenogram showed

evidence of obstruction at the esophagojejunal junction (Fig. 6). On esophagoscopic examination an apparently benign anastomotic stricture was found. Biopsies failed to reveal malignant change. When viewed with the activating light, no fluorescence could be detected. Subsequent surgical exploration revealed extensive metastasis within the abdomen with a metastatic mass compressing the terminal portion of the esophagus. This case illustrates the necessity of reaching the malignant lesion with the activating light in order to cause fluorescence of the accumulated derivative.

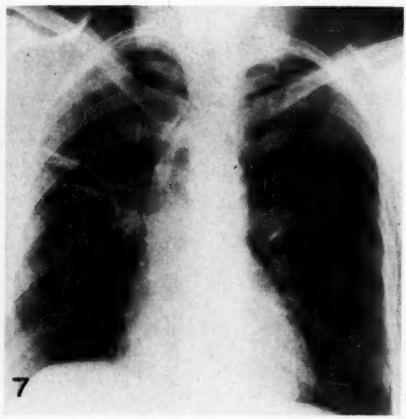

Fig. 6.—(Case 4). View of esophagus and jejunum showing obstruction at the esophagojejunal junction.

Fig. 7.—(Case 7). View of thorax showing mass in hilus of right lung with obstructive pneumonitis in the right upper lobe.

A roentgenogram of the thorax of a patient known to have had carcinoma of the breast (Case 7) showed evidence of a mass in the right hilus with obstructive pneumonitis in the right upper lobe (Fig. 7). Bronchoscopic examination revealed stenosis of the right main bronchus at the level of the right upper lobe, with considerable bronchial deformity. When viewed with the activating light, the region in question showed considerable fluorescence. Biopsies revealed metastatic scirrhous adenocarcinoma (grade 4). As mentioned previously, the patient exposed herself to direct sunlight, despite our admonition, and a transient photosensitivity reaction developed.

COMMENT

The use of hematoporphyrin derivative and fluorescent endoscopy in the 15 cases described has demonstrated for the first time what may well prove to be a valuable adjunct in the detection of cancer. The method is completely flexible and readily lends itself to all forms of endoscopy.

Once the patient is properly prepared, the only prerequisite for the success of our method is for the activating light to reach the involved region in sufficient intensity. If the light cannot reach the lesion, then naturally there can

be no fluorescence. However, with the great gains that are being made in the field of glass-fiber optics, many new applications of our technique may become available.

It is too early to say just how reliable the utilization of hematoporphyrin derivative and fluorescent endoscopy will prove to be in the differentiation of malignant from benign lesions. However, if it does no more than delineate the regions involved by neoplasia, whether benign or malignant, and thereby aids the clinician in deciding where to obtain a specimen for biopsy, it will be of great value.

With improved endoscopes it appears that this method of cancer detection will be employed in many different parts of the body.

SUMMARY

Our experience with the use of hematoporphyrin derivative and fluorescent endoscopy leads us to believe that a new aid for the detection of malignant disease has been developed. Fifteen patients have been studied thus far. Neither false-positive nor false-negative results developed among the patients in whom a sufficient amount of the activating light reached the region of involvement. Although our experience with the technique is not extensive, it appears that this new technique will be a valuable adjunct for the detection of malignant disease.

We are indeed grateful to Mr. Merlin Neher for his assistance in the design and construction of equipment used in this study.

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(For Discussion, see page 637.)

LUNG RESECTION WITH TEMPORARY VASCULAR AND BRONCHIAL OCCLUSION

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SURGERY in any area is made difficult and even hazardous if a film of blood covers the field. In the lung the problem is magnified when air bubbles up through this film to produce an obscuring foam. Thus, lung resections of less than a lobe are often crude and imprecise. Large clamps which are generally used for wedge resections or the stapling device recently advocated[1] avoid the bloody foam but they remove normal lung tissue along with the disease in a gross and deforming manner. Segmental resections done with conventional technique are rarely as accurate and neat as the surgeon hopes they will be; lung disease is not limited by segmental boundaries and, in any case, the lung is not neatly segmental. Regions between the segments seem about as bloody as any other part of the lung, and there is plenty of air to stir up the obscuring foam. Experience teaches the surgeon how to get along with these problems, after a fashion. Despite the bloody foam, blood loss is not great and he soon learns to move along rapidly through the messy parts of these operations. Nevertheless, he may recognize that his surgery lacks accuracy—an accuracy which may be necessary for some types of lung disease and which could improve any type of sublobular resection.

This accuracy may be achieved quite easily in a bloodless field and this bloodless field can be obtained in the lung by simply occluding the hilus, the same way it is obtained in the hand by compression of the arm. Orthopedic surgeons operate routinely in a bloodless field and the principle of occluding blood flow through an operative field has found application in other regions, such as the heart and the brain. Why has it not found more frequent use in the lung?

Lung root occlusion was used many years ago[1,2] as a method of controlling the hilus when the lung was to be resected. More recently a few surgeons

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have advocated lung root occlusion to facilitate certain types of resections, particularly resections of pulmonary arteriovenous fistulas. In a discussion of a paper on pulmonary arteriovenous fistulas, Crafoord[7] recommended occlusion of the pulmonary vessels and the bronchus to achieve a bloodless field. Subsequently, Blades and his associates[3, 4, 5] made some important studies of lung ischemia because of its possible application in bloodless surgery and for autografting or homografting. They suggested that 30 minutes was probably the safe limit of vascular occlusion with complete functional recovery. On the basis of this experimental work, Blades occluded the lobe hilus in 7 patients undergoing segmental resections. He employed an occlusion technique in which the pulmonary artery and vein were occluded, but in which the bronchus and bronchial artery remained open for a maximum occlusion period of 20 minutes. A few other surgeons have studied lung root occlusion or used it clinically. In the excision of a pulmonary arteriovenous fistula, Parker and Stallworth[10] occluded the pulmonary artery and vein, and later Bosher[6] employed the same technique for the same lesion. Hankinson[9] studied the tolerance of the lung of the dog to ischemia and concluded, on the basis of experiments in 16 dogs, that it would stand an hour of ischemia without damage. In a rather unusual but rational application of lung root occlusion, Baffes[2] reported in 1960 that he routinely occludes the pulmonary artery, and apparently the bronchus too, when reversing the attachments of the right pulmonary veins and the inferior vena cava in his operation for complete transposition of the great vessels. Temporary pulmonary venous occlusion is required in this operation so complimentary pulmonary inflow occlusion would be sensible.

EXPERIMENTAL WORK

The experimental work, some of which has been published elsewhere,[8, 11] is summarized in Tables I and II. To begin with, several operations on dogs were used to devise a satisfactory way of obtaining a completely bloodless lung. The best technique was a staged occlusion of the hilar structures combined with overinflation of the lung. First the pulmonary artery was clamped, then the lung was overinflated during each inspiration by increasing the inspiratory pressure to about 30 mm. Hg; this was continued for 5 minutes. Finally, at the height of an inspiration, the bronchus and pulmonary veins were occluded. Very little blood remained in the lungs which were occluded in this fashion. Wedge resections were done in each case to make certain that the lung was ischemic.

The experimental studies showed that either the lobe or the entire lung will withstand an hour to an hour and a half of ischemia without developing gangrene or any apparent damage. Only 1 of 19 animals succumbed (Table I). Two out of 3 animals recovered after 4 hours of occlusion at normal temperature but 6 hours of occlusion was fatal. Regional cooling of the lung increased its tolerance to ischemia, however, so that all of 5 animals subjected to 6 hours of lung ischemia while the lung was at 10° C. survived.

After recovery from the operation in which ischemia was produced, a contralateral pneumonectomy was done in 20 of the animals as a test of the functional capacity of the lung which had been ischemic. The results, which are summarized in Table II, suggest that the lung made ischemic for an hour at normal temperature regained satisfactory function. Lungs which had been ischemic for several hours at reduced temperatures failed in some instances to support the animal. Three of the 5 animals in which the remaining lung had been subjected

to 6 hours of ischemia at 10° C. did survive, however. Patency of the bronchial arteries in the 19 animals subjected to one to one and a half hours of ischemia was checked by postmortem angiography. In every case the arteries were patent.

The experimental work showed that the normal dog lung will withstand at least an hour of complete vascular and bronchial occlusion at normothermia with functional recovery. On this basis we have applied the technique to clinical use. Although regional hypothermia lengthened the tolerable occlusion period to several hours in the dog, we have not believed that it was necessary in the clinical cases.

TABLE I. LUNG ISCHEMIA: SURVIVAL IN DOGS*

EXTENT	TEMPERATURE	OCCLUSION PERIOD (HR.)	NUMBER	DEATHS
Lobe	Normal	1	8	0
Left lung	Normal	1-1½	11	1
Left lung	37° C.	4	3	1
Left lung	37° C.	6	4	4
Left lung	25° C.	2	3	0
Left lung	25° C.	4	3	1
Left lung	25° C.	6	4	1
Left lung	10° C.	2	2	0
Left lung	10° C.	4	1	0
Left lung	10° C.	6	5	0

*Experiments described in previous publications.[8, 11]

TABLE II. CONTRALATERAL PNEUMONECTOMY AFTER LUNG ISCHEMIA IN DOGS*

TEMPERATURE	ORIGINAL OCCLUSION PERIOD (HR.)	NUMBER	DEATHS
Normal	1-1½	4	1
37°C.	4	2	0
25°C.	2	3	0
25°C.	4	2	2
25°C.	6	2	2
10°C.	2	2	2†
10°C.	6	5	2

*Experiments described in previous publications.[8, 11]
†Deaths attributable to technical errors.

CLINICAL APPLICATION

In 19 patients who required various types of sublobar lung resection during the past 2½ years, we have occluded the lung root for periods of 12 to 70 minutes. In the first 7 patients we used the method which was most effective for producing a dry field experimentally. The pulmonary artery was occluded first and then, after a 5-minute period of over-ventilation, the bronchus and the veins were occluded. This provided a very satisfactory bloodless field, but a hilar dissection was required. To eliminate the necessity for this dissection, we had a special clamp made (Fig. 1) which will occlude the entire lung root at once; we have used this clamp in the last 11 operations. In one operation (Case 4), a Satinsky clamp was used to occlude the hilus of a lobe. When the large clamp is used it is first put in position with the throat of the clamp superiorly so that the bronchus will be located at the strongest part of the clamp. Then the lung is overdistended to an intratracheal pressure of about 40 mm.

Hg in order to force blood out as the clamp is closed. Although the lung may not be quite as dry as with individual clamping of the hilar structures, we now prefer the large root clamp. It is easy to use but the jaws must be tightly closed or bleeding will occur from the cut lung surface. When a lip of lung parenchyma was inadvertently included within the jaws, thus preventing satisfactory closure, troublesome bleeding occurred during a recent segmental resection.

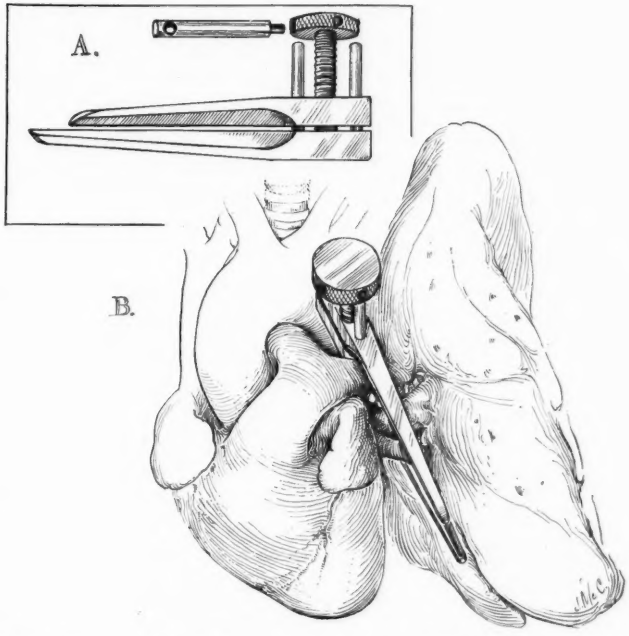

Fig. 1.—*A*, Large clamp which is used to occlude the hilus of the entire lung. *B*, This drawing shows application of the clamp at the hilus of the left lung.

Once the hilar structures have been occluded, the diseased lung tissue is grasped and simply cut out. At this point, no attention is paid to the vessels or to the bronchi. The field is dry and the surgeon directs all his attention to an accurate and careful excision of the diseased tissue. During operations for emphysematous blebs as many as six or eight areas of disease have been removed. After the excision, the visible bronchi and vessel ends are grasped with hemostats and tied with 3-0 silk. This leaves a raw surface which would still leak a large amount of air unless something further is done. In most of the operations, some or all of the raw surface has been closed by suturing the edges of the lung wound together with continuous catgut, and in 11 of the patients we used surface electrocoagulation[11] to seal all or part of the lung wound. It may produce less distortion and functional crippling than suturing does,

but it produces a rather thick scar and, too, air leaks may be difficult to seal with electrocoagulation alone. Electrocoagulation may find its best use in destroying the tiny blebs which occur along the edges of the lung in emphysema. To seal effectively the larger surfaces, we have used absorbable cellulose* in one case. This may prove to be more effective than cauterization and less deforming than suturing.

Table III is a summary of our clinical experience with lung hilar occlusion. Three types of patients have been operated upon: 8 patients with emphysematous blebs, 7 patients known to have tuberculosis preoperatively, and 4 patients with "coin" lesions—all of which turned out to be infectious granulomas. There was one death 2 days postoperatively in a 48-year-old man (Case 2); a myocardial infarction was identified as the cause of death at postmortem. This man's poor pulmonary function was doubtless a contributory cause, however. The lung which had been subjected to 50 minutes of ischemia and multiple bleb resections showed severe congestion at autopsy. We cannot tell if the technique of lung hilar occlusion contributed to the congestion found in this lung, but, of course, it may have.

The most troublesome postoperative complication has been persistent air leak which occurred in 4 of the patients who underwent resection of emphysematous blebs. In one of these (Case 7), a catheter which remained in the chest for 3 weeks finally eroded the left subclavian artery and an emergency thoracotomy was required in order to control the hemorrhage. This patient, who had been severely disabled due to his emphysema and who had earlier undergone resection of blebs on the other side by conventional technique, ultimately obtained an excellent result. The patients who had persistent air leaks postoperatively finally had the tubes removed without developing empyema pockets after as long as 30 days of intrapleural suction. Persistent air leak is liable to be a troublesome problem no matter what technique is used for multiple resection of blebs in an emphysematous lung; it is not a special complication of the root occlusion technique. Air leaks did not occur in the patients with tuberculosis or "coin" lesions.

Although all the patients with emphysema and most of the others had undergone preoperative testing of pulmonary function, not enough of them had undergone postoperative tests of pulmonary function to help us in evaluating the technique. In one patient (Case 1), pulmonary function test done only 4 weeks after operation showed some reduction in vital capacity, although the maximum breathing capacity was unchanged. In another patient (Case 9), evaluated 2 months after operation, there was no change in pulmonary function. We would expect changes in pulmonaray function after surgery to be related to the extent of the resection and the nature of the lung disease and not to the use of temporary ischemia, but further study of this matter is necessary.

*Surgical cellulose—Johnson & Johnson, New Brunswick, N. J.

TABLE III.

CASE NO.	AGE	RESPIRATORY FUNCTION	DATE	OPERATION			REMARKS
				LUNG OCCLUSION			
				TYPE	TIME (MIN.)	RESECTION	
A. EMPHYSEMATOUS BLEBS							
1	39	Poor	8 /11/58	Individual	30	Apical subsegments	Uncomplicated
2	48	Poor	9 /17/58	Individual	50	Multiple subsegments	Died 2 days postop.; myocardial infarction
3	37	Fair	12/ 4/58	Individual	50	Multiple subsegments	Uncomplicated
4	40	Fair	11/ 6/59	Root clamp	15	Lobectomy plus subsegments	Uncomplicated, had tuberculosis too
5	31	Fair	12/30/59	Individual	55	Multiple subsegments	Air leak—3 weeks
6	51	Poor	5/16/60	Root clamp	45	Multiple subsegments	Air leak—18 days; pneumothorax 4 weeks postop.
7	46	Poor	1/19/61	Root clamp	15	Multiple subsegments	Air leak—3 weeks; subclavian artery hemorrhage
8	46	Good	2/ 1/61	Root clamp	45	Multiple subsegments	Air leak—30 days
B. TUBERCULOSIS							
9	30	Fair	7/ 3/58	Individual	30	Apical posterior and superior segments	Uncomplicated; complications followed resection of opposite side later by conventional means
10	40	Good	8/ 4/58	Individual	30	Apical posterior segments	Uncomplicated
11	45	Good	12/19/58	Individual	45	Apical posterior segments	Uncomplicated
12	31	Good	2/23/60	Root clamp	30	Apical posterior segments	Uncomplicated
13	38	Good	9/28/60	Root clamp	30	Superior segments	Wound infection
14	27	Good	9/30/60	Root clamp	70	Multiple subsegments	Uncomplicated
15	44	Fair	1/12/61	Root clamp	12	Upper lobectomy; lower subsegments	Planned 2nd stage thoracoplasty done
C. "COIN" LESIONS							
16	46	Good	5/ 9/60	Clamp	15	Subsegment	Uncomplicated
17	45	Good	11/18/60	Clamp	20	Subsegment	Wound infection
18	49	Good	3/ 1/61	Clamp	15	Subsegment	Uncomplicated
19	42	Good	3/17/61	Clamp	30	Subsegment	Uncomplicated

In one patient (Case 17), pulmonary artery pressure and blood gas levels were measured during and after a 20-minute period of lung root clamping. Pulmonary artery pressure rose slightly to 38/10 mm. Hg during clamping, in comparison to levels of 30/10 before and after clamping. Carbon dioxide content rose slightly during clamping but the other blood gas levels were unchanged.

DISCUSSION

The experimental work and our preliminary clinical experience disclose no penalties for the benefits a surgeon gains by using temporary lung ischemia. Apparently, the lung withstands ischemia for relatively long periods without damage, and with regional cooling this period of tolerable ischemia may be extended beyond practical need. By simply clamping the lung root firmly, the thoracic surgeon can have the quiet, bloodless field essential for painstaking work which the surgeon who operates on the hand uses routinely. The concept is simple, rational, and apparently sound. Clamping has not torn the vessels and thrombosis has not developed. Bronchial arteries have remained patent in the animals in which they were inspected. The site at which the bronchus was clamped has not caused trouble. Potentially, we suppose, these various points could be the source of difficulty. Rough application of the clamp could injure the pulmonary vessels and clamping of the bronchus could cause an intrabronchial hemorrhage or a scar. Clearly, our experience is not yet great enough to justify an unreserved recommendation of the technique.

In some of the patients, atelectasis has been quite troublesome, and, in 2 of the patients undergoing resection of "coin" lesions, the pleural reaction evident on x-ray examination seemed to be more than we usually encounter in operations of this magnitude. Could these problems be a consequence of the hilar clamping technique? We do not know.

The problem of air leak in the cases of bleb resection, described above, is, in our minds, related to the disease and the technique of lung surface closing rather than to the hilar clamping. Successful surgery for emphysema requires multiple resections which leaves large raw surfaces; if any part of this raw surface remains open, or if it opens up postoperatively, a troublesome air leak may occur. To avoid extensive suturing of the lung, we have employed electrocautery in some cases, but this has not been entirely satisfactory since it does not seal the lung surface in the emphysematous human lung as well as it did in the normal dog lung. Absorbable cellulose may provide a better method. In addition to a firm surface closure, adequate, postoperative, intrapleural suction is needed and we have not always been successful in providing it. The technical problems of both lung wound closure and postoperative suction need further study.

Hilar occlusion may find other applications. We have used it to perform resections for "coin" lesions, but it seems to offer no advantage over a wedge resection with clamps. Hilar clamping was used many years ago for lobectomy and it might be taken up again for this operation, in combination now, with individual treatment of the hilar structures. We have not tried it, however, for slippage of the clamp could be a serious hazard and there would appear to be no advantage over conventional techniques for this resection.

SUMMARY

1. Experiments in dogs indicate that the normal lung will withstand an hour of ischemia at normal temperature and several hours at lowered temperature without damage.

2. In 19 patients, 8 of whom had emphysematous blebs, 7 of whom had tuberculosis, and 4 of whom had "coin" lesions, we used a technique of hilar occlusion in order to obtain a bloodless operating field. With a large, specially designed clamp all the hilar structures may be effectively occluded at once.

3. The one death in the clinical series was attributed to postoperative coronary artery occlusion. Complications have been similar to those that occur after conventional lung surgery.

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DISCUSSION

(PAPERS BY ESMOND [PAGE 563], WILSON [PAGE 575], WARE [PAGE 580], CANTRELL [PAGE 589], CAMISHION [PAGE 599], GERST [PAGE 607], BEATTIE [PAGE 615], LIPSON [PAGE 623], AND LEWIS [PAGE 630] AND THEIR ASSOCIATES)

DR. HENRY SWAN, II, Denver, Colo.—We certainly would agree with Dr. Cantrell when he says that the history of attempts to create a tracheal substitute have been fraught with difficulties. We would also agree that, whenever possible, it would be desirable not to use a prosthesis if one could possibly use a primary anastomosis, as he did so beautifully in the case illustrated.

However, I would like to report a more encouraging experimental effort on behalf of my colleague, Dr. David Kramitch, [slide] who used a Teflon prosthesis in corrugated shape, a corrugated tube, as the basic prosthetic device. He found that he had very great success in the lack of irritation with this device but very great difficulty in keeping it in place. Therefore, he devised the system of using Marlex mesh which is a different plastic and very irritating. The use of this to create fibrosis around the anastomosis between the trachea and the prosthesis was very successful and he now has 4 dogs in each of two groups which I will show you, that are alive over 12 months.

[Slide] Here is just the detail of the anastomosis with the Marlex mesh to stimulate fibrosis.

[Slide] In dogs in whom seven to ten rings had been removed and replaced by the prosthesis, here is one at 7 months. The dog is quite healthy. This same animal is now 13 months along and still equally healthy.

[Slide] Another type of experiment is one in which the entire right lung was removed, together with the carina and nine rings of the trachea, and the prosthesis was used from the trachea to the left bronchus. All of these dogs are living over 12 months, so this is encouraging. It appears that it is at least possible in the dog to make a plastic prosthetic tracheal substitute which serves as a functional normal airway for at least a year.

DR. ELLIOTT MICHELSON, Baltimore, Md.—We have tried internal prosthetics but, because of the unpredictability of this method, have become interested in methods of tracheal elongation. Harris (Thorax 14: 176, 1959) showed that in man, when the neck is extended, the trachea is lengthened approximately 2.5 cm., and with deep inspiration the carina descends another 2.5 cm. so that at least 5 cm. extension is possible. By mobilizing the cervical and thoracic trachea, Barclay (Thorax 12: 177, 1957) was able to bridge a 6 cm. gap.

Som (J. Mt. Sinai Hosp. 25: 211, 1958) has attempted to elongate the trachea by incising the annular ligaments in the intercartilagenous spaces, but this gives no appreciable increase in length. We (Michelson et al., J. THORACIC SURG. 41: 748, 1961) have tried to increase the length of the trachea by incising the right inferior pulmonary ligament, releasing the trachea from the left main bronchus at the carina, and anastomosing the left main bronchus to the right bronchus intermedius. In recently autopsied cases, we noted that, under the age of 50 years, incising the inferior pulmonary ligament lengthened the trachea by 2.5 to 3 cm. and an additional 3 cm. was obtained by freeing the left main bronchus. In those over the age of 50, approximately 4 cm. increase could be obtained.

We repeated this experiment in 6 dogs and found that, after resecting 18 to 20 tracheal rings, anastomosis without tension could be accomplished by incising the inferior pulmonary ligament, dividing the left main bronchus at the carina, and anastomosing the left main bronchus to the right upper lobe or to the right bronchus intermedius. Four dogs died because of technical difficulties but 2 lived without respiratory difficulty until sacrificed 6 months later. Bronchoscopy and autopsy revealed the suture lines to be well healed with no decrease in the lumen of the trachea.

We would suggest, in addition to the extension of the trachea normally possible by mobilization, that incision of the right inferior pulmonary ligament and division of the left main bronchus at the carina will allow 9 to 10 cm. elongation.

DR. ARTHUR C. BEALL, JR., Houston, Texas.—We, as everyone else, will agree that whenever possible, primary anastomosis is the ideal technique to use in the presence of a tracheal defect.

We also agree with Dr. Swan that on certain occasions it is necessary to use some type of prosthesis, and we have attempted to use Marlex mesh as such a prosthesis.

[Slide] We have created seven-ring circumferential defects in the cervical tracheas of mongrel dogs, replacing the defects with tubes of Marlex mesh with the use of interrupted Marlex sutures.

[Slide] This is the open prosthesis at 9 months. We now have some of these dogs that have survived well over a year.

[Slide] This shows that the Marlex is originally covered with squamous epithelium overlying a basal cell layer.

[Slide] This is followed shortly by minute nests of columnar epithelium within the squamous layers.

[Slide] At 9 months most areas are covered by columnar-type, respiratory appearing epithelium.

Having followed the dogs with cervical tracheal defects over a year, we believe that with such defects Marlex mesh appears to be a satisfactory prosthesis.

We have now done this with thoracic tracheal defects. I am sorry the results are preliminary as yet but, if they continue to be encouraging, we hope to make a formal presentation on this work at a later date.

DR. FREDERICK H. TAYLOR, Charlotte, N. C.—In tracheal restoration, we used one other technique. [Slide] This is a primary cylindroma of the trachea at about the suprasternal notch which was resected in a 54-year-old man and an end-to-end anastomosis was done. Three inches of trachea were removed with the aid of mediastinotomy which allowed for good mobilization of the trachea.

[Slide] You can see the suture line. We used rather heavy silk there, 2-0 silk, which looks like rope in this picture, and I think the use of stainless steel wire may have merit because, 4 weeks after surgery, three of these sutures had to be removed through the bronchoscope. Six months later the patient has a good airway with no recurrence of tumor.

DR. WILLIAM S. BLAKEMORE, Philadelphia, Pa.—The paper of Dr. Camishion is of interest to us since we have been doing studies with a little different emphasis. We have measured total cardiac output before, during, and after the atelectatic period. In these studies we found a decrease in the blood flow to the atelectatic lung, although the cardiac output varied considerably.

There are other factors to be considered in the interpretation of these data. The effect of positive pressure anesthesia under these circumstances, as Dr. Gerst showed in his paper may cause the cardiac output to be lowered. The lung that is atelectatic is not under positive pressure so that the differential of flow through the atelectatic area may be more when the chest is open than when it is closed.

When at the time of operation the patient is turned to the lateral decubitus position, the collapsed lung is the upper lung and the lower lung will get preferential blood flow due to the higher hydrostatic pressure. The effect of atelectasis in the upper lung would presumably be less under these circumstances.

DR. E. E. ROCKEY, New York, N. Y.—Bronchogenic carcinoma in the dog was produced by us in December, 1956, by repeated applications of cigarette smoke condensate to the bronchial mucosa. Carcinoma in situ was also produced in March, 1957.

Results of these experiments were presented in May, 1958, at the New York Society for Thoracic Surgery. Reference was made to the findings by Dr. Dean F. Davies in a paper published in June, 1960, in the *Journal of Chronic Diseases*, and by Dr. David T. Carr in a paper published on June 22, 1960, in the *Proceedings of the Staff Meetings of the Mayo Clinic.*

By means of tracheal fenestration, we have been applying cigarette smoke condensate to the bronchial mucosa of 116 dogs, some of which have been observed over a period of 4 years. We have produced carcinoma in situ in 2 dogs, and invasive carcinoma in 1 dog. This study is being continued, and the maximum changes found in the dogs treated with cigarette smoke condensate range from precancerous changes to carcinoma in situ and invasive carcinoma. None of these changes has occurred in the 140 control animals, and it is our firm belief that invasive carcinoma of the lung can be produced in the dog by the carcinogenic agents in cigarette smoke condensate.

Although our study differed in purpose and method from that conducted by Dr. Beattie and his associates, I believe a report of our findings is relevant and in order. (Slides showing carcinoma in situ and invasive carcinoma were presented.)

DR. R ADAMS COWLEY, Baltimore, Md.—With reference to Dr. Lewis' paper, there are one or two questions I want to ask. First of all, with the lung collapsed, how do you know how much to take out and from where to take it?

Also, although it does speed up the operation considerably, I wonder how long air leaks persist, and if it increases the hospital stay of these patients.

This is the first time, other than the von Petz clamp, that I have seen a wrench used to tighten a clamp, and I wonder about the end result, whether there is bronchial crushing and whether long-term follow-up studies have shown bronchial stenosis resulting from the use of such a clamp.

DR. CANTRELL (Closing).—Dr. Michelson's point is exceedingly well taken. Mobilization is absolutely essential if primary anastomosis is to be accomplished in significantly long defects.

I might say, however, that we had no intention of implying that this is *the* method of tracheal repair. It is limited in the extent to which it may be applied and there are various conditions which affect this. Fibrosis, inflammation, or any other condition of the trachea which affects its ability to stretch under tension will limit the applicability of the method. Age is another consideration.

In the small series of tracheas obtained at autopsy, we have found that, in patients over 80 years of age, no more than two tracheal rings may be resected without exceeding the limit of tension which we have found permissible in the dog.

I would congratulate Dr. Beall and Dr. Swan on the results which they have obtained but I would like to point out that long-term survival per se is not a suitable criterion of success. The nylon prosthesis shown in our slides was removed from that dog at approximately 9 months. The dog appeared clinically well at that time, but you saw the totally unsatisfactory results. The most impressive aspect of Dr. Beall's results is the presence of epithelization. It would be essential to know whether or not this was present over the entire area of the prosthesis, since complete covering must be considered a prerequisite to permanent success. One of his slides suggested that this might not be true.

DR. CAMISHION (Closing).—If any flow determination is made within the first 30 to 45 minutes following collapse of one lung, the results are apt to be unpredictable. The reasons for this are fully discussed in the paper.

We found that, when the bronchus was occluded with a metal clamp, the metal in close proximity to the electromagnetic probe caused an apparent immediate drop in blood flow. We found that this occurred consistently. Therefore, in all our experiments the bronchus was ligated with a cotton tape which did not affect the magnetic field.

DR. BEATTIE (Closing).—I do not wish to have any controversy about priority. I do think if Dr. Rockey has created cancer in the dog it would be very valuable to make a report of it himself in the JOURNAL. I think, though, that what we need is a method to study the pathogenesis of bronchogenic carcinoma. We believe that our yield of three cancers in 8 animals in 12 months may be important.

DR. LEWIS (Closing).—In answer to Dr. Cowley's first question about how we decide what to take out and what to leave in, we try, of course, to take out the diseased areas of the lung and leave in the normal areas of the lung [laughter]; this does, of course, take some experience, maturity, and judgment.

As some guide, usually the tuberculous areas can be palpated as indurated areas. The blebs have various identifying features. The larger ones look something like tired football bladders. The smaller ones often have the consistency of cotton candy, though there is also a strikingly different pigmentation.

The normal lung is pink whereas the emphysematous area is quite a bit darker.

Actually, having a bloodless, airless field does not detract; it actually aids in identifying the disease.

So far as increased complications are concerned, we cannot tell from a mere 19 cases whether complication rates are higher than they are by conventional techniques. We

have been bolder, I think, in excising blebs with this technique than we ever were before. Since we have time and a quiet field in which to deal with all these raw areas, I think the main problem is that of closing all the raw areas and we have not yet solved it satisfactorily.

So far as bronchial stenosis and such complications are concerned—we might expect to produce bronchial stenosis, we might expect to tear vessels, we might get thrombosis in these vessels, but these complications have never occurred. There, again, 19 cases are too few.

There were 20 dogs in which we studied the bronchial artery after this occlusion and in no case was the bronchial artery damaged or occluded. We have not studied nerve function to see if that has been damaged.

A NONSUTURE METHOD OF ANASTOMOSIS OF THE LEFT INTERNAL MAMMARY ARTERY TO THE CORONARY ARTERY

George J. Magovern, M.D. (by invitation), Edward M. Kent, M.D., Bernard S. Levowitz, M.D. (by invitation), Ram S. Ratan, M.D. (by invitation), John B. Lovette, M.D. (by invitation), Sheldon O. Burman, M.D. (by invitation), and Vernon Orwig, B.S. (by invitation), Pittsburgh, Pa.

THE established techniques of vascular anastomosis are attended by a high incidence of thrombosis when applied to small caliber vessels. This has been a major deterrent to the extension of these techniques to the coronary vessels and, thereby, a deterrent to augmentation of coronary blood flow by direct methods. In an attempt to establish a feasible method of both small vessel anastomosis and augmentation of coronary flow, we have modified a technique of internal mammary artery to coronary artery anastomosis,[1] originally described by Carter and Roth.[2] This paper is primarily concerned with the results in 5 animals which have been observed 12 to 18 months following this procedure.

METHOD

Mongrel dogs weighing from 15 to 20 kilograms were used in the study. They were anesthetized with pentothal sodium, respirations were maintained with a Jefferson ventilator, and using sterile procedure, a standard left thoracotomy was used. The left internal mammary artery was dissected free from its origin down to the sixth intercostal space, and all branches were carefully dissected free and ligated with 4-0 arterial silk suture and transected. The internal mammary artery was then occluded at the brachiocephalic artery with a bulldog clamp, and distally was ligated with a 2-0 silk suture. It was then transected at approximately the sixth intercostal space and a second bulldog clamp was placed on the distal end of the freed internal mammary artery. Two cubic centimeters of a heparin solution (1 mg. per 100 c.c.) was injected into the intervening segment. The distal end of the vessel was prepared by removing the adventitia and then threaded through the lumen of either a polyethylene or nylon stent. The polyethylene stent is no longer used, and

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*From the Department of Surgical Research, University of Pittsburgh School of Medicine, and the Allegheny General and Presbyterian Hospitals, Pittsburgh, Pa.

subsequently will not be described. The nylon stent developed in this laboratory is shown in Fig. 1, *A* and *B*. It is machined from a nylon bar, and stents from 2 to 5 mm. in internal diameter were used. The wall thickness of the stents was approximately 0.5 mm., except at its most distal point where they are

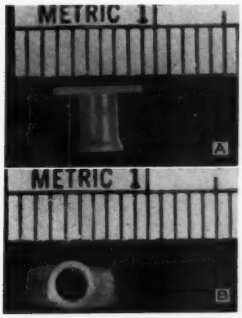

Fig. 1.—Nylon stent which was used in all cases of long-term survival.

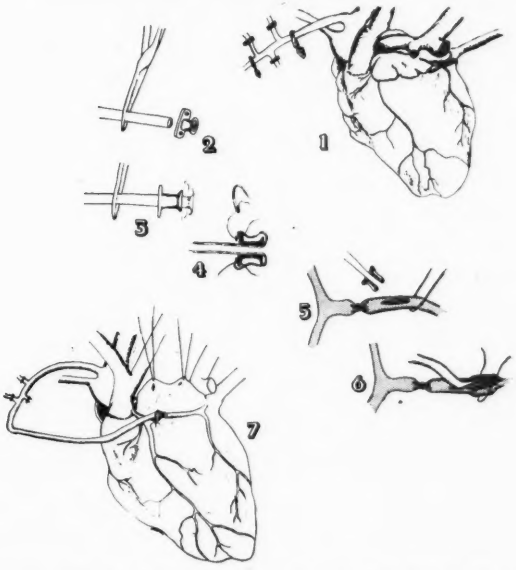

Fig. 2.—Graphic representation of the method of preparation and anastomosis described in detail in the text.

slightly flared. The proximal end of the stent contains two flanges which were used for fixation of the vessel. After the vessel was threaded through the lumen of the stent, it was everted in a cuff-like manner over the stent and fixed to the flares with 4-0 silk sutures. The distal end of the vessel and stent were then dipped in mineral oil to prevent drying and to aid the ease of insertion into the circumflex artery. The pericardium was then opened, the left atrial appendage

was retracted, and the circumflex artery identified. It was dissected free for a distance of 1 cm. at its origin from the left coronary artery, and two 4-0 silk ligatures were placed around the vessel. The proximal ligature was tied at the origin of the circumflex branch and the distal ligature was then drawn taut to

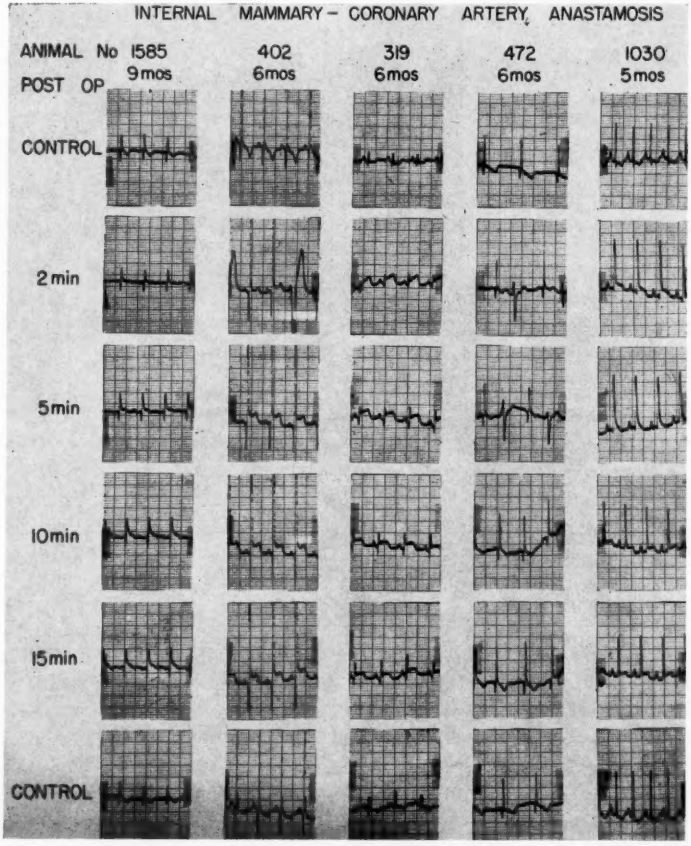

Fig. 3.—This figure shows serial Lead II electrocardiograms which were taken on the 5 long-term survivors at the second thoracotomy. Note the S-T segment elevation and the ectopic foci indicative of myocardial ischemia during temporary occlusion of the internal mammary artery and return to base line following release.

prevent reflux bleeding. A transverse incision was made in the circumflex artery, and the prepared internal mammary was inserted into it, thereby achieving an intima-to-intima approximation. The silk ligature was tied over this point of approximation (Fig. 2).

RESULTS

Twenty-six animals were used in the experiment. Group I consisted of 7 animals in which a polyethylene stent was employed. These animals were subsequently followed for 2 to 22 weeks, and all showed thrombosis at the site of

anastomosis. The second group comprises 19 animals in which the technique as outlined was employed. Eleven animals were observed for a period of up to 3 months. One animal died in 24 hours with infarction. Six animals were followed from 2 to 11 days and sacrificed; all showed a patent anastomosis. Four animals died in a period of 5 to 11 weeks, and all showed a patent anastomosis.

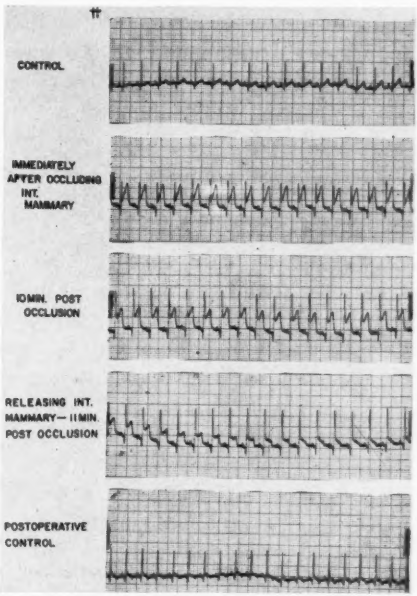

Fig. 4.—No. 1585. Serial electrocardiogram Lead II taken before, during, and after occlusion of the internal mammary artery a year and a half following internal mammary to coronary artery anastomosis. The marked S-T elevation is indicative of a functioning patent anastomasis.

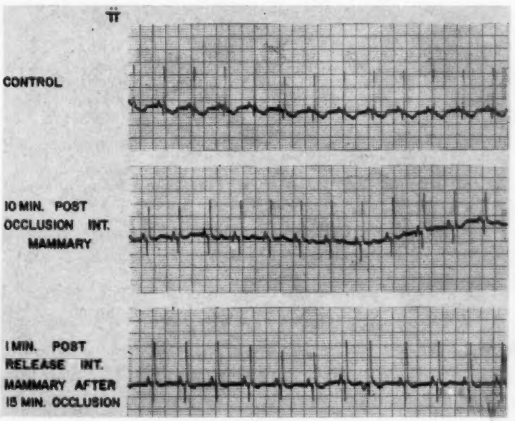

Fig. 5.—No. 472. Angiocardiogram and serial electrocardiogram made 15 months after left internal mammary to coronary artery anastomosis. Both indicate a patent and functioning anastomosis.

Long-term observations were made in 5 animals which were followed over a period of 14 to 18 months, and in 3 other animals which were observed from 1 to 5 months and, when sacrificed, showed a patent anastomosis. The 5 animals comprising the long-term observation were subject to two subsequent thoracotomies, at which time electrocardiographic and angiocardiographic studies were obtained. The angiocardiograms were obtained by placing a catheter into the brachiocephalic artery proximal to the origin of the internal mammary and injecting 3 c.c. of a 25 per cent Urokon solution. Evidence of a patent anastomosis was obtained in all animals at the first study, and in 4 of the 5 animals in the subsequent thoracotomy.

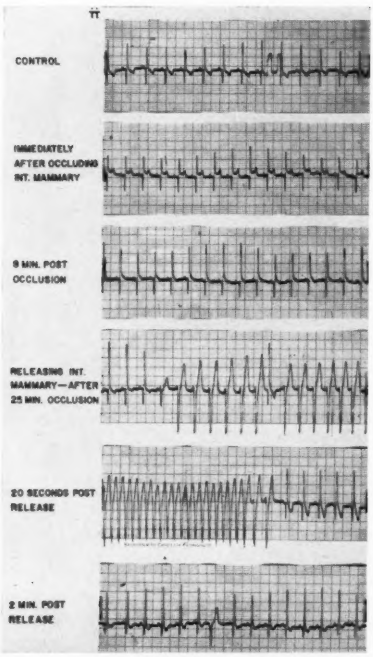
CONTROL
IMMEDIATELY AFTER OCCLUDING INT. MAMMARY
9 MIN. POST OCCLUSION
RELEASING INT. MAMMARY—AFTER 25 MIN. OCCLUSION
20 SECONDS POST RELEASE
2 MIN. POST RELEASE

Fig. 6.

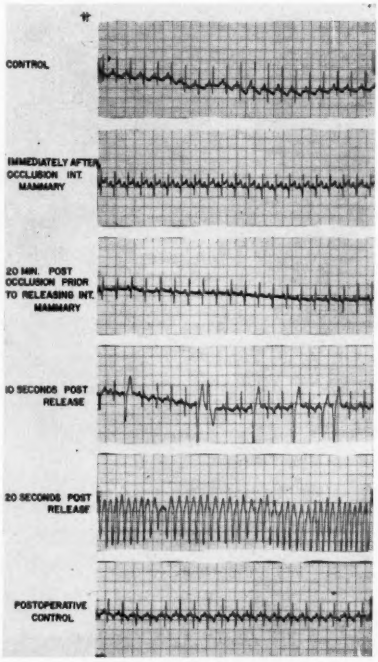
CONTROL
IMMEDIATELY AFTER OCCLUSION INT. MAMMARY
20 MIN. POST OCCLUSION PRIOR TO RELEASING INT. MAMMARY
10 SECONDS POST RELEASE
20 SECONDS POST RELEASE
POSTOPERATIVE CONTROL

Fig. 7.

Figs. 6 and 7.—Nos. 402-319. Serial electrocardiogram Lead II taken 15 months after anastomosis. Note the S-T elevation noted during temporary occlusion of the internal mammary artery. Note the dramatic ventricular tachycardia following release of the clamp, indicating the marked electrical phenomena which may develop with unevenly distributed myocardial flow.

After angiocardiography, a serial electrocardiogram was obtained during 2, 5, 10, and 15 minutes of occlusion of the internal mammary artery. The progressive evidence of myocardial ischemia, as illustrated by S-T segment elevation and the development of ectopic foci, are shown in Fig. 3. These animals were again studied 9 months later by an identical technique. One animal after this intervening period no longer had a patent anastomosis. The remaining 4 animals were demonstrated to have a patent and functioning anastomosis. All animals are still alive. The longest survivor, at 18 months, showed more

pronounced ischemic changes than were produced by the previous study (Fig. 4). A second animal showed definite changes following occlusion, but tended to exhibit evidence of adequate collateral circulation as shown by reversion of the S-T segment of the base line after 10 minutes of internal mammary occlusion. Angiocardiography, however, showed a patent anastomosis at this time (Fig. 5). The remaining 2 animals, 15 months after surgery, also exhibited a functioning anastomosis as illustrated in Figs. 6 and 7. However, attention is drawn to the dramatic changes immediately following release of the occlusion of the internal mammary artery. One sees many ectopic beats and ventricular tachycardia which appears to be on the verge of ventricular fibrillation. We believe that this represents dramatic evidence of the electrical phenomenon which may develop following unequal distribution of the myocardial blood flow, thereby causing ventricular fibrillation and death without demonstrable coronary occlusion or myocardial infarction.

SUMMARY

A method of nonsuture anastomosis employing a plastic stent was performed in 26 animals. A polyethylene stent was used in 7 animals, and all showed thrombosis within a 3-month period. A nylon stent was used in 19 animals. They were observed for varying periods of time, and 17 of the 19 animals at the time of sacrifice, death, or, when studied, showed patent anastomoses.

Five of these animals were restudied at 13, 15, 15, 15, and 18 months, respectively, after their original operation. Four of the five long-term observations showed a patent and functioning anastomosis. The technique of employing the internal mammary and the circumflex coronary artery points out a possible method for clinical application in those patients with proximal occlusion of a coronary vessel. The technique, however, would depend on adequate preoperative coronary artery visualization.

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(For Discussion, see page 702.)

EFFECTS OF CONTINUOUS FLOW THROUGH IMPLANTED MAMMARY ARTERY AND MYOCARDIAL ISCHEMIA ON MAMMARY-CORONARY COMMUNICATIONS

M. Lopez-Belio, M.D. (by invitation), Salvador Rodriguez, M.D. (by invitation), H. C. Stansel, M.D. (by invitation), George Tasaki, M.D. (by invitation), F. Gomez-Ferrer, M.D. (by invitation), and O. C. Julian, M.D., Ph.D., Chicago, Ill.

EXPERIMENTAL methods of increasing the volume or effectiveness of coronary blood flow include those which cause a redistribution of flow within the coronary artery system without necessarily bringing more blood from extracardiac sources and those which provide a new source of blood from an extracardiac area. It is likely that the effectiveness in changing internally the dynamics of coronary flow by causing an irritative epicarditis and pericarditis is due to opening up of intercoronary communications. This view has been largely put forth by Beck[1] who increased the efficiency of the irritative lesion in producing intercoronary communications by partially obstructing the venous outflow from the myocardium, presumably thereby causing additional dilatation of communicating vessels between elements of the right and left coronary arterial system. The methods by which additional sources of blood may be brought from extracardiac areas include, among others,[2, 3] the technique of Vineberg[4] who implanted the internal mammary artery in a tunnel of myocardium without making direct communications to the coronary system. Methods of anastomosis of a systemic artery directly to the coronary artery are described by Murray,[5, 6] Thal,[7] Julian,[8] and Moore.[11]

Experimental work in myocardial revascularization is complicated by a variety of factors, particularly in regard to the evaluation of the effectiveness of indirect methods. It has been pointed out by Vineberg and others that an important requirement for effectiveness of simple mammary artery implantation is the development of myocardial ischemia which may be considered a stimulant to the development of communications between the implanted mammary artery and the coronary arterial system. A second most important consideration in indirect methods which bring additional blood supply from extracardiac

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sources is the fact that redistribution of flow within the heart may result from the irritation of the procedure. It seems possible that this factor could seriously affect evaluation experiments using survival following acute coronary ligations or measurement of retrograde circumflex artery flow after ligation of the vessel as a criterion.

An attempt was made by the authors in 1955[9] to overcome in part some of these difficulties by devising a method of myocardial revascularization in which the implanted mammary artery was kept open by connecting it to the mammary vein, producing a long loop incorporating an arteriovenous fistula. This then was implanted in the myocardium. The artery was thought necessarily to remain open, allowing a maximum opportunity for the development of communications. Comparison of the results in instances in which the artery did not remain open with those in which the preparation succeeded in this regard controlled to some extent the factor of the effect of the intrapericardial procedure on intercoronary communications. In this work, however, the end-to-end mammary-arteriovenous fistula was found to close in 21 out of 26 experimental animals. In the five preparations in which the artery remained open, observations suggested development of communications between the implanted fistula and the coronary system. The factor of previously induced myocardial ischemia was not a part of that study.

Another method has since been sought by which the implanted mammary artery could be depended upon to remain open. The further modification of the Vineberg mammary artery implantation used in the present experiment consists of a transplantation of the origin of the vessel from its normal location to a point on the descending thoracic aorta, the latter anastomosis being made after passing the vessel through a myocardial tunnel. Observations made using this preparation are to be presented. They concern the development of connections between the implanted vessel and the coronary artery system in relation to the degree to which the lumen of the implanted vessel remains open and in relation to previously induced myocardial ischemia.

METHODS

Two procedures were used in preparing animals for study in various groups. These are (1) the production of chronic myocardial ischemia by partial ligation with a cotton ligature of the circumflex branch of the left coronary artery, and (2) the implantation of the reconnected internal mammary artery into a myocardial tunnel.

Partial ligation of the circumflex branch of the left coronary artery was carried out at a point 1 mm. from the bifurcation of the left coronary artery. The septal branch of the left coronary artery was identified and was never included in the partial obstruction. After isolating the vessel at this point, a No. 20 cotton ligature was passed around it and tied securely over an interposed metal probe, 0.6 mm. in diameter (Fig. 1). A mild diffuse cyanosis was frequently observed at this point. However, if cardiac irregularities began to develop, the ligature was cut away and, after the cardiac action became stable, re-applied. As will be noted in the presentation of results, the circumflex coronary artery at the point at which it is partially tied in this manner with a cotton ligature tends predominantly to become occluded completely, but in some instances remains only partially obstructed. The influence of the development of partial or complete occlusion on the results will be discussed.

The transplantation of the origin of the internal mammary artery was simplified by excising a cuff of the subclavian artery with the end of the vessel. The subclavian artery was then simply ligated and the internal mammary artery freed from its branches and the surrounding tissues downward to the level of the seventh costal cartilage. The myocardial tunnel was produced by the passage of a blunt end probe, 3/16 of an inch in diameter, through the left ventricular myocardium. The tunnel was made along a line between the circumflex and anterior descending branches of the left coronary artery (Fig. 2). The tunnel varied from 4 to 7 cm. in length and was at a depth estimated to be approximately half the thickness of the left ventricular wall. The freed mammary artery was then passed from the apical end of this tunnel upward and laterally to the basilar end of the tunnel. It was brought through the myocardium far enough to provide a length of free vessel which would reach, without tension, the most convenient point in the descending thoracic aorta. This area of the descending aorta was sufficiently cleared for the application of a partially excluding curved clamp, and the anastomosis of the vessel end-to-side, utilizing the cuff of subclavian artery, was then done using a continuous fine silk suture. The branches of the internal mammary artery were tied with fine cotton ligatures before division. No patent branches were carried into the tunnel.

Four groups of animals were prepared and studied. Group A consisted of 10 dogs in which the internal mammary artery, left to its normal attachment, was simply implanted into a tunnel, such as that described above, after detaching its distal end downward for the same distance. All of the branches of this mammary artery were ligated and the distal end of the vessel was also ligated. This preparation, which was used to control the production of a myocardial tunnel and the pericardiotomy, differs significantly from the standard Vineberg implantation of mammary artery in that the branches of the mammary artery were ligated. The second group (B) consisted of 28 animals in each of which the mammary artery loop, which has been described, was produced. Groups C and D, made up of 11 animals each, were first subjected to the partial coronary occlusion at the proximal end of the circumflex branch of the left coronary artery as described. This initial procedure was done 6 weeks prior to the mammary artery implantation which in Group C was similar to the control Group A, and in Group D consisted of the continuous flow mammary loop as in control Group B.

Two additional groups of animals were studied for further control. One of these, consisting of 10 animals (Control Group I), was subjected to the studies about to be described without any prior experimental preparation. The second (Control Group II) consisted of 10 animals in which partial occlusion of the circumflex branch of the left coronary artery had been produced 6 weeks before sacrifice and study.

At the time of evaluation, the heart was re-exposed through a left chest incision with the dog under barbiturate anesthesia. Preoperative medication consisted of morphine and atropine, and the anesthesia was induced with 12 mg. of Nembutal per kilogram 30 minutes after the premedication had been given.

The anterior descending and the circumflex branches of the left coronary artery were isolated; an 18 gauge needle or a polyethylene tube having identical internal diameter was then introduced through the anterior wall of the aorta 1.5 cm. from the aortic valve. This was used to gather samples of blood for determination of its oxygen content and for continuous recording of the pressure existing at the coronary ostia. If the pressure at this level showed a tendency to fall, as it did only occasionally, the pressure was supported by the intravenous infusion of 5 per cent dextrose in water. Drugs were not used to support the arterial pressure.

The left coronary artery was then acutely ligated without, at this time, making any critical observation as to whether the previous partial ligation had become complete in those animals in which this had been carried out. The distal end of the circumflex coronary artery

was cannulated, and backflow was measured at intervals during the ensuing hour and calculated in milliliters per hour. The pressure exerted by the backflow was measured and the oxygen content of the blood obtained was determined. The incidence of ventricular fibrillation during the one-hour period following acute ligation of the circumflex coronary artery was recorded. No attempt was made to restore sinus rhythm to those hearts which fibrillated in this period.

The animals that survived without ventricular fibrillation for one hour following acute ligation of the circumflex coronary artery were then subjected to acute ligation of the anterior descending branch of the left coronary artery. The measurements pertaining to

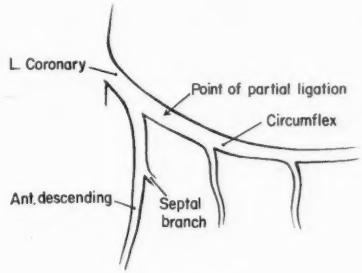

Fig. 1.—See text.

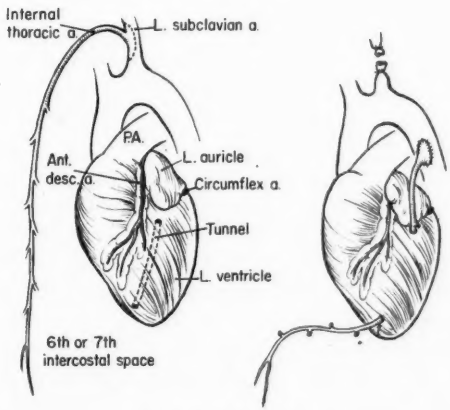

Fig. 2.—See text.

pressure and oxygen content of blood at the coronary ostia, and of backflow from the distal end of the circumflex coronary artery were repeated. Each observation was continued for a period of one hour following this ligation of the anterior descending branch. The occurrences of ventricular fibrillation during this one-hour period were recorded.

The animal was sacrificed at the conclusion of the second hour in those cases in which heart action was still present. The specimen of heart and mammary artery was removed for x-ray and histologic study. The implanted mammary artery was visualized by x-ray studies postmortem. For this x-ray examination a saturated potassium iodide solution was injected into the mammary artery at a pressure equal to the mean arterial pressure which had existed at the proximal end of the aorta during the period of evaluation.

RESULTS

Observations made in all groups of the pressure and oxygen content of blood at the coronary ostia (Table I) serve to demonstrate that, under the conditions of the animals at the time of study, the pressure supplied to blood entering the coronary system was adequate and at comparable levels in all groups, and also that its oxygen saturation was adequate and similar throughout the experiment.

TABLE I. AVERAGE PRESSURE AND O_2 CONTENT OF BLOOD AT CORONARY OSTIA IN ANIMALS SURVIVING EACH STAGE OF EVALUATION

GROUP	LIGATION OF CIRCUMFLEX ARTERY		LIGATION OF ANTERIOR DESCENDING ARTERY	
	PRESSURE (MM./Hg)	O_2 CONTENT (%)	PRESSURE (MM./Hg)	O_2 CONTENT (%)
Control I	96	21.82	—	—
Control II	90	22.41	—	—
A	—	—	—	—
B	90	18.6	—	—
C	92	18.83	88	18.91
D	96	20.66	90	20.41

The incidence of ventricular fibrillation during a one-hour period of observation following acute ligation of the circumflex branch of the left coronary artery and the characteristics of backflow from the distal end of the ligated vessel are shown in Table II. In Control Group I, the animals having no previous preparation, one of the 10 animals survived this period, and a backflow of 144 c.c. per hour was calculated, the backflow blood having an oxygen content of 19.3 vol. per cent in this one animal. The pressure exerted by the backflow was 11 mm. of water. Control Group II, consisting of 10 animals, showed an incidence of ventricular fibrillation during this one-hour period of 4 animals, or 40 per cent. The rate of backflow in the 6 surviving animals averaged 378 c.c. per hour at an average pressure of 24 mm. of water and the oxygen content of this backflow blood averaged 20.7 vol. per cent. No animal of the 10 comprising Group A, in which simple implantation of the mammary artery had been done, survived the one-hour period. In Group B, 6 of the 28 animals, prepared by the continuous flow technique, survived the hour. These showed a backflow at an average rate of 216 ml. per hour at a pressure of 38 mm. of water and an arterial oxygen content of 18.2 vol. per cent.

TABLE II. LIGATION OF CIRCUMFLEX CORONARY ARTERY (1 HR.)

GROUPS	CIRCUMFLEX BACKFLOW			ONE-HOUR SURVIVORS	
	ML./HR.	PRESSURE ($CM./H_2O$)	O_2 (VOL. %)	NO.	%
Control I (10)	144	11	19.3	1	10
Control II (10)	378	24	20.70	6	60
Group A (10)	—	—	—	0	0
Group B (28)	216	38	18.2	6	22
Group C (11)	614	64	18.15	6	55
Group D (11)	570	64	20.31	8	73

Eleven animals of Group C had been prepared by simple implantation of the mammary artery 6 weeks after the production of a partial occlusion of the circumflex coronary artery. Of these 11 animals, 6 survived acute ligation of the circumflex artery; the backflow from the distal end of the vessel in these 6 survivors averaged 614 ml. per hour at a pressure of 64 mm. of water. The oxygen content of this blood was 18.15 vol. per cent. In Group D, consisting of 11 animals having implantation of continuous flow mammary artery loop 6 weeks after partial circumflex artery ligation, 8 animals survived. These showed an average backflow of 570 ml. per hour at a pressure of 64 mm. of water and an oxygen content of 20.31 vol. per cent.

The animals surviving the hour following circumflex artery ligation were subjected immediately to acute ligation of the anterior descending branch of the left coronary artery. The survivors in which this second ligation was done represented one animal in Control Group I, 6 of Control Group II, 6 of Group B, 6 of Group C, and 8 of Group D. No survivors remained in Group A to be studied in this second phase.

During the one hour of observation following this second acute ligation (Table III), 2 of the 6 animals remaining in Group C and 6 of the 8 animals remaining in Group D survived. Fibrillation followed this second ligation in all of the remaining animals of the other groups.

TABLE III. ACUTE ANTERIOR DESCENDING LIGATION IN ONE-HOUR SURVIVORS OF CIRCUMFLEX LIGATION

GROUP AND NO.	ML./HR.	PRESS. (CM. H_2O)	O_2 (VOL. %)	O_2 AORTA	ONE-HOUR SURVIVORS	
					THIS PHASE	TOTAL EXPER.
Group C					2	
6	182	21	17.63	18.91		18%
(11)					33%	
Group D					6	
8	246	31	18.89	20.41		55%
(11)					75%	

The backflow studies in the 2 and 6 animals of Groups C and D, respectively, are specifically referred to in Table III. In Group C the backflow was at an average rate of 182 ml. per hour, an average pressure of 21 cm. of water, and the oxygen content of the blood was 17.63 vol. per cent. In Group D, the average backflow was 246 ml. per hour, at an average pressure of 33 mm. of water and an oxygen content of 18.89 vol. per cent.

The data obtained by observations during these two one-hour periods following acute ligation first of the circumflex artery and second of the anterior descending coronary artery serve to indicate the value of the various preparations in protection against ventricular fibrillation. The further study of the specimens concerned the degree of obstruction of the circumflex artery which had actually been produced by its previous partial ligation in those animals in which this was done, the degree of patency of the internal mammary artery in

those animals in which it had been implanted in one of the two ways, and the relationship of these entities to the survival or failure to survive of the various animals through the sequence of acute ligations.

Table IV shows the results of these anatomic studies. Control Groups I and II are not included in this table, because the mammary artery had not been transplanted.

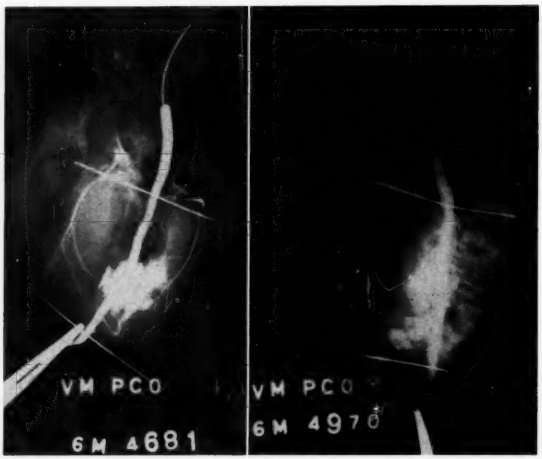

Fig. 3.—Radiographic films produced by injection of contrast medium into mammary artery in 2 animals of Group D 6 months after preparation. Collateral filling of the coronary system is shown.

TABLE IV. ANATOMIC STUDY: COMMUNICATIONS VS. PATENCY OF MAMMARY AND PRIOR ISCHEMIA

GROUP	% HAVING PATENT MAMMARY	OBSERVED STATE OF pCO (%)		MAMMARY-CORONARY COMMUNICATION PRESENT
		COMPLETE	PARTIAL	
Group A (10)	50	0	0	20% (2)
Group B (28)	64	0	0	20% (6)
Group C (11)	81	91	9	54% (6)
Group D (11)	100	82	18	82% (9)

A certain incidence of connecting vessels between the implanted mammary artery and the coronary artery system was demonstrated by x-ray examination in each group. In Table IV, the proportion of animals showing the development of collateral vessels refers only to the individual animals of each group in which the mammary artery was open. In those animals having occlusion of the mammary artery, injections of the contrast medium could not in the first instance have been done. Study of the circumflex artery occlusion in terms of the previous partial ligation of the vessel indicated that either a partial or complete occlusion was present at the time of study in all animals of Groups C and D, and that complete occlusion predominated in both groups. Both patency and collateral artery formation were improved in animals with simple implantation by the prior production of myocardial ischemia as shown by a comparison of

Groups A and C. The same was true in regard to the continuous flow preparation as shown by Groups B and D. Anatomic demonstration of collaterals between mammary and coronary systems depended upon the visualization by x-ray studies of the coronary system after injection of Diodrast into the

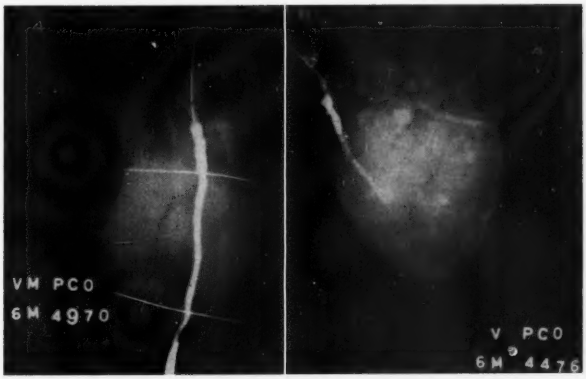

Fig. 4.—Roentgenogram of animal of Group D showing absence of collaterals to the coronary system. This dog failed to survive the second ligation.

Fig. 5.—Roentgenogram of animal of Group C showing faint visualization of coronary vessels. Animal failed to survive ligations.

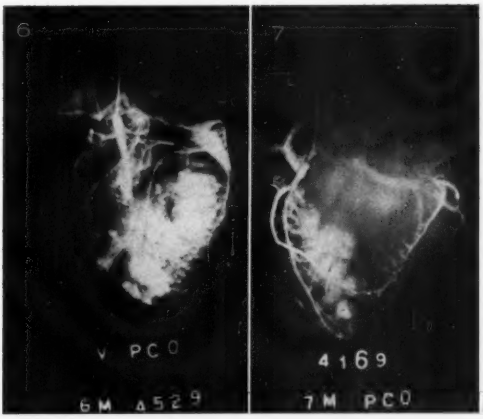

Fig. 6.—Roentgenogram of animal of Group C. This animal shows extensive filling of coronary vessels through the simple mammary implant.

Fig. 7.—Injection was made in this animal of Control Group II through the anterior descending branch. The circumflex branch was found to be entirely occluded and the filling seen is by way of intercoronary communications.

mammary artery under the pressure conditions mentioned. Two examples in which visualization of the coronary system by mammary injection indicates the presence of such collaterals are shown in Fig. 3 in animals of Group D. Fig. 4 is the radiographic film made after injection of the mammary artery in an animal of Group D which failed to survive the second ligation, that is, acute

ligation of the anterior descending branch. Fig. 5 is the radiogram resulting from injection of Diodrast into the implanted mammary artery in an animal of Group C in which the mammary artery was found to be open, although irregular, and filling of the left coronary artery system is shown, although not in great concentration. This animal failed to survive the acute ligations. Fig. 6 is another example of a simple implantation of the mammary artery with more extensive filling of the coronary system through the implanted vessel.

Fig. 7 is the roentgenogram of an animal in Control Group II, being one of the animals that survived for one hour following acute ligation of the circumflex coronary artery. This animal, together with all other members of this group, failed to survive the subsequent acute ligation of the anterior descending coronary artery. This roentgenogram was made by the injection of Diodrast into the anterior descending coronary artery just beyond the point at which it had been acutely ligated with the production of ventricular fibrillation. This radiograph (Fig. 7) shows the development of intercoronary communications leading to channels on the posterior aspect of the heart.

HISTOLOGIC STUDIES

Histologic examination of all of the implanted arteries, whether the method of implantation was by continuous flow loop or by the method of Vineberg, was carried out in a limited number of segments of each vessel in both its extracardiac and intramyocardial course. During this examination it was first of all noted that there was no discrepancy between the demonstration on arteriography of patency of the mammary artery and the histologic demonstration of patency. During the course of examination of these segments, it became evident that nothing short of serial sectioning with a high concentration of slide evaluation would add very much to the x-ray evaluation of the lumen. This limitation arises from the fact that a mammary artery under these conditions may be possessed of a wide lumen in one area and a significantly narrowed lumen in another. It is also notable that, although apparent branch formation was observed, there was no single section studied which contained in continuity the mammary artery lumen and the lumen of a branch sufficiently long to be undeniably a newly formed vessel which could be establishing communication to a pre-existing myocardial blood vessel. It was observed that closure of the implanted vessel occurred both by fibrosis and thickening of the implanted vessel wall and by thrombosis. Throughout the sections studied, the most normal appearing arteries were those which had been implanted in such a way as to provide for continuous flow. There was a general absence of perivascular inflammation or fibrosis in the tissues surrounding the implanted mammary artery. Reaction to its presence consisted of the formation of granulation tissue containing many small blood vessels. Inasmuch as these almost certainly arise from the pre-existing myocardial vessels, their presence indicates that an opportunity exists for the formation of mammary-coronary communications, although none was demonstrated in sections.

DISCUSSION

Unless some factor exists which has entirely escaped the notice and consideration of ourselves and others who have studied the implantation of a systemic artery into the myocardium, it appears from these observations that the heart of the dog possesses the ability to adapt which may be considered to be under specific observation. The adaptation phenomenon concerned is the formation of branches from a vessel placed in this new course which make communications with the surrounding native vascular bed. The occurrence of this phenomenon is indicated by these experiments both on the functional basis in changing the response of the heart to subsequent acute coronary ligations and the anatomic demonstration that an x-ray opaque substance injected at the pressure observed to be present in the vessels during the experiment into the implanted vessel is accompanied by the appearance of the substance in the native vessels. The conclusion that the channel by which this communication occurs is related to the lumen of the implanted artery and not to smaller vessels, such as vasa vasorum or granulations growing down the implanted vessel, depends on the following consideration in the results. The protection afforded by implantation of a mammary artery is governed by the presence of a lumen in the implanted vessel. Only those animals having a significant lumen showed a difference in protection against ventricular fibrillation as compared to animals having a prior pericardiotomy for the purpose of partial ligation of the circumflex coronary artery alone.

Except for one technical consideration the relationship between prior partial ligation of the circumflex coronary artery (and the resulting assumed ischemia) and the effectiveness of the implanted mammary artery, if it remains open, has been demonstrated. The reservation arises from the obvious fact that, other than for the implantation of the artery, those animals with mammary transplant plus prior partial ligation of the circumflex artery and the animals with partial ligation only differ also in the fact that, at the time of testing, the latter group has had one less thoracotomy and pericardiotomy than the former. Except for this reservation, the thesis is supported that previous partial ligation of the circumflex coronary artery does result in a greater degree of development of a source of blood supply from the implanted vessel.

Some early experiences in our laboratory with the technique of mammary artery implantation itself suggests a pitfall in the study of such preparations. It is essential that the mammary artery be implanted in such a manner that it is not twisted in the myocardial tunnel and is not kinked or stretched in its course to or from the tunnel when the heart is allowed to return to its normal position. The vessel itself in these experiments was thinned as much as possible by the removal of adventitia. The possibility that this is important in formation of communications is only conjectural.

An outstanding difference between all of the implantations done in this experiment and those done by Vineberg is the fact that all of the mammary artery branches were ligated in this experiment and the end of the vessel was ligated when a continuous flow loop was not done. The Vineberg preparation differs

in that these openings in the vessel are allowed to remain. If communications had failed to form under the conditions of the present experiment, the negative results would have been valueless and the preparations would have had to be repeated, leaving the branches unligated.

The results of the present experiment cannot be construed to mean that the animals prepared by a continuous flow loop of mammary artery implanted in the myocardium in the presence of previous myocardial ischemia could have been revived for long survival after ligation of the main branches of the left coronary artery except its septal branch. As the conclusion of the two one-hour periods of study was reached in those animals in which ventricular fibrillation did not occur, a greater and greater number required the infusion of fluids to maintain blood pressure, and, although the myocardial contractility was not measured, it appeared grossly to deteriorate. Also, it cannot be concluded that these animals would have survived the simultaneous ligation of the two branches of the coronary artery, a test which can be assumed to be a more trying one than the sequential ligation as done in this experiment.

Although mammary artery implantation has been used clinically and promising results reported, it is not presently our intention to so use the modification of the Vineberg operation described in this work.

SUMMARY

1. An experimental procedure consisting of implantation of the dog's left internal mammary artery into a myocardial tunnel in the left ventricle, in such a manner as to provide for the continued normal function of the artery, has been used to test the factors of continuous flow through the implanted artery and of pre-existing myocardial ischemia in these preparations.

2. The effectiveness of an implanted artery in becoming an extracardiac source of coronary circulation was tested by observing the effect of subsequent acute ligation, first, of the circumflex branch and, second, the anterior descending branch of the left coronary artery. These tests were made during periods in which the continued heart action maintained a satisfactory aortic pressure at the level of the coronary ostia, sometimes with the aid of infusions of 5 per cent dextrose in water. During the period in which these ligations were done, the pressure and volume of backflow from the distal end of the tied circumflex artery, the oxygen content of this blood, and the incidence of ventricular fibrillation were recorded.

3. Several groups of experimental animals and controls were studied. The controls consisted of animals (Group I) having no preparation prior to the evaluation experiment and animals (Group II) in which partial ligation of the circumflex coronary artery was done 6 weeks prior to evaluation. The experimental groups were (Group A) 10 animals in which a Vineberg type of implantation of the mammary artery was done with the modification that all of the branches and the distal end of the vessel had been tied; Group B—28 animals in which the mammary artery was transplanted into a myocardial

tunnel in such a fashion as to provide for its continued normal function; Group C—animals in which the modified type of Vineberg procedure was done 6 weeks following a primary procedure in which the proximal end of the circumflex branch of the left coronary artery was partially tied; and Group D—11 animals in which the continuous flow type of mammary loop was implanted 6 weeks after partial circumflex artery ligation.

4. The evaluation experiments done in these groups of animals indicate by the incidence of fibrillation, the volume of backflow from the ligated circumflex artery, and anatomic studies by arteriography, that previously induced myocardial ischemia and good patency of the implanted vessel affect the development of communications between the implanted vessel and the native coronary circulation, almost to the point of being essential factors.

5. Histologic studies of the implanted arteries support the radiographic observations in regard to patency. They showed that when the implanted artery became obstructed, it was due to fibrosis and thickening of the vessel wall and to thrombosis. Microscopic studies failed to demonstrate morphologically the communicating branches of the implanted vessel.

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(For Discussion, see page 702.)

SURGICAL CORRECTION OF CORONARY ARTERIOVENOUS FISTULA

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APPARENTLY Krause[35] in 1865 was the first to describe a coronary arteriovenous fistula in which a large anomalous branch of the pulmonary artery communicated with a plexus of vessels involving the right coronary artery. We wish to present a study of 73 patients,[1-65] including 2 new patients with congenital coronary arteriovenous fistula. Levine[36] has recorded a patient presenting a traumatic coronary arteriovenous fistula. Excellent recent summaries have been presented by Steinberg[52] and Gasul[28] and their associates.

Most of these patients are asymptomatic in early life unless there is a major left-to-right shunt. Patients range in age from 3 weeks[28] to 84 years.[49] Symptoms include (a) varying degrees of cardiac failure, (b) angina (apparently rare), and (c) endocarditis (also rare). Rupture has not been reported. Massive enlargement has been reported by Valdivia[55] and Scott[49] in the postmortem examination of 2 patients in whom the aneurysms measured 17 by 23 by 14 cm. and 10 by 8 by 8 cm., respectively. These aneurysmal sacs were filled with laminated clot.

Most commonly a cardiac murmur or the roentgenographic evidence of an enlarged or abnormally contoured heart was the initial symptom. In approximately 85 per cent of the cases the murmur was continuous in type, heard maximally in two thirds of the cases at the lower right or left parasternal areas. However, in one third of the reported cases, the continuous murmur has been maximal in the upper left parasternal area, the region of the classical patent ductus murmur. Gasul[28] has commented on the ability of the Valsalva maneuver to diminish more significantly the murmur of intracardiac than extracardiac fistulas, although ductus arteriosus may also show diminution or absence of the diastolic component upon the application of this maneuver. Phonocardiography has been stressed as an aid in differential diagnosis by Gasul[28] who states "phonocardiographic demonstration of a louder diastolic than systolic component is very suggestive of a coronary arteriovenous fistula communicating with the right ventricle."

In 20 cases of proved coronary arteriovenous fistulas, the continuous murmurs were studied by phonocardiography. In 12 patients the murmur was

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found maximal elsewhere than in the left upper parasternal region. The diastolic component predominated in 8 patients and 4 showed predominance of the systolic component. In 8 patients the continuous murmur imitated the "classical patent ductus murmur," at least in regard to location on auscultation. In 5 such cases, the phonocardiogram revealed the greater intensity to be diastolic, suggesting a fistula other than patent ductus. However, in three instances the murmur was classically located and had the systolic predominance expected of a persistent ductus arteriosus.

Further analysis reveals that the position of maximum intensity of the murmur may show a distinct correlation with the chamber into which the fistulous communication emptied. Two fistulas emptying into the pulmonary artery had maximal continuous murmur over the pulmonic area. Two of three fistulas involving the right atrium were maximal in this region. Seven of ten communications with the right ventricle were maximal over a lower sternal region.

Intracardiac phonocardiography has been used with some success in the differential diagnosis of the cause of continuous murmurs, including coronary arteriovenous fistulas.

ROENTGENOGRAPHIC CHANGES

The use of roentgenograms and fluoroscopy may be nonrevealing in low-flow left-to-right shunts. In larger shunts enlargement of the chambers subjected to increased flow by the abnormality may occur. In some instances there may be increased pulmonary vascular markings and increased pulsations of the pulmonary arteries. Bizarre contours of the cardiac chambers due to saccular or cirsoid aneurysmal changes have been noted. Three authors, Gasul,[28] Biorck,[10] and Knoblich[34] have stressed the importance of dilatation of the ascending aorta. Unquestionably, the greatest value of radiography lies in the application of angiocardiography. When performed by the venous route or by local injection into the right side of the heart, the findings reveal only the site of emptying of the fistula. Significant flow into the right atrium or into the right ventricle may decrease the intensity of the shadow of the contrast medium in the vicinity of the inflow of the blood which does not contain contrast material. This has been alluded to as a local "black-out phenomenon" or, by Gasul,[28] as a "blanching phenomenon." Retrograde arteriography has been described in recent years by several authors.[11, 41, 52, 61-63] In some instances retrograde angiography has been misinterpreted as indicating the presence of a rupture of the sinus of Valsalva. This error should be obviated if the retrograde aortogram is done in two planes, as with the Elema equipment or if cineangiography equipment is utilized.

ELECTROCARDIOGRAPHY

Electrocardiographic studies are nonspecific. Significant ventricular hypertrophy or strain may be considered an urgent indication for surgical intervention. The presence of a small shunt with no evidence of ventricular hypertrophy or strain and a normal roentgenographic study may justify a further period of observation.

CARDIAC CATHETERIZATION

Cardiac catheterization is useful when the shunt empties into the cardiac veins, right atrium, or ventricle. It may be confusing even in these instances and may suggest a septal defect. It can be completely confusing when the fistula communicates with the pulmonary artery or the upper portion of the right ventricular outflow tract. It is of no value in shunts emptying into the left heart, except in that it may reveal elevation of pulmonary artery pressure. Certainly, it is useful in evaluating the physiopathology present. In the studies which have been reported, the degree of left-to-right shunt has been found to vary from 0.67 L. per minute per square meter to as high as 6.43 L. per minute per square meter. In only two instances the shunts were greater than the systemic flow.

SITES OF FISTULOUS COMMUNICATION

Adequate details describing the nutrient arterial component and the chamber into which it drained were presented in 55 of the reported cases (Table I). In many instances the blood was not flowing directly into the chamber involved but into coronary veins forming a cirsoid mass, or into a large saccular aneurysmal component which communicated with the chamber involved. The arteries and chambers involved are presented in Tables II and III.

TABLE I. REPORTED SITES OF CORONARY ARTERIOVENOUS FISTULS*

CORONARY ARTERY INVOLVED					
RCA	LCCA	LAD	L. CIR. A	ABERRANT	COMMUNICATING WITH
6	0	0	0	2	R. atrium (8)
10	1	8	1	5	R. ventricle (25)
3	4	0	0	1	Pulmonary artery (8)
0	0	2	0	0	L. atrium (2)
0	0	0	0	3	L. ventricle (3)
5	2	0	2	0	Coronary sinus (9)

*In 18 of 73 cases these data were incomplete.

TABLE II. CORONARY ARTERIOVENOUS FISTULAS

INCIDENCE OF SPECIFIC ARTERY INVOLVEMENT	
ARTERY	NUMBER
Right coronary artery	29
Left coronary artery (30)	
a. Common	7
b. anterior descending	12
c. circumflex	3
d. aberrant branch	8
Both coronary arteries	2
Not specified	12
Total	73

REVIEW OF PAST SURGICAL EXPERIENCES

In 1947, Biorck and Crafoord[1] reported the first successful operation for coronary arteriovenous fistula in which an anomalous branch of a left coronary artery communicating with the pulmonary artery was ligated. The preoperative diagnosis was persistent ductus arteriosus. The patient made an uneventful

TABLE III. CORONARY ARTERIOVENOUS FISTULAS

INCIDENCE OF SPECIFIC CHAMBER INVOLVED	
CHAMBER	NUMBER
Right atrium	19
Right ventricle	26
Pulmonary artery	9
Left atrium	3
Left ventricle	3
Single ventricle	1
Not specified	12
Total	73

recovery. Since that time, 27 patients have been operated upon. In reviewing their records, we find that, until the advent of the increased use of retrograde aortography, the preoperative diagnosis was uniformly incorrect. In two instances a direct vision operation, utilizing the pump-oxygenator, was planned because the retrograde aortogram was interpreted as showing a ruptured sinus of Valsalva. The value of the Elema biplane study or cineangiography has previously been mentioned.

The indications for surgery are presented in Table IV. Eleven patients presented a continuous thrill, 16 a continuous murmur, 5 a systolic murmur alone, and 3 a separate systolic and diastolic murmur. The radiologic abnormalities included increased activity of the pulmonary arteries (3 cases), enlargement of the pulmonary artery (3 cases), right atrial enlargement (4 cases), right ventricular hypertrophy (5 cases), left ventricular hypertrophy (6 cases), enlarged ascending aorta (5 cases), and progressive heart enlargement (4 cases).

TABLE IV. REPORTED SURGICAL CASES

INDICATIONS FOR SURGERY	NUMBER
Significant murmur(s)	27
Radiologic findings (static)	23
Radiologic findings (progressive)	4
Symptoms	
a. frequent lung infection	3
b. angina	1
c. persistent cardiac failure	1

Note: the majority of cases were originally misdiagnosed.

The absence of symptoms in this group reflects the frequency with which operation was planned because of the preoperative diagnosis of persistent ductus arteriosus. In our patient (Case 2) the initial exploration was due to a faulty diagnosis, but 7 years later she had developed significant angina pectoris on effort.

The operations employed are presented in Table V. In 2 cases, Fell[24] added to ligation of the artery an incision into the aneurysmal sac and ligation of the fistulous tract with subsequent suture obliteration of the aneurysmal sac. Swan[53] performed the sole aneurysmorrhaphy with ligation of the fistulous tract and reconstruction of the lumen of the involved vessel. The postoperative course in this instance was described as "stormy." Beck, as reported by Mozen,[39] ligated an aberrant branch of the left anterior descending coronary

artery, described as 1.5 cm. in length and 0.5 cm. in diameter, which appeared to empty directly into the left atrium. Bahnson[8] recently operated upon a patient with a lesion in which a branch of the right coronary artery drained directly into the right atrium. He was able to dissect out the communication directly at the point of entry into the atrium without sacrificing any part of the right coronary arterial system. This patient made an uneventful recovery. Kittle[27] encountered an aberrant vessel emptying into the left auricular appendage and corrected the defect by amputation of the left auricular appendage.

TABLE V. REPORTED SURGICAL CASES

TYPES OF OPERATION UTILIZED	NUMBER
Ligation coronary artery (12)	
a. alone	10
b. plus transaneurysmal ligation of fistula	2
Ligation aberrant artery	8
Ligation fistula alone	3
Endoaneurysmorrhaphy	1
Unspecified	3
Total	27

Note: Nine additional patients underwent exploratory thoracotomy alone.

In all but 2 of the 27 cases, a "clinical cure" was obtained. The complications attending these procedures are enumerated in Table VI. In the report by Amplatz[6] of his fourth case, a severe bradycardia and hypotension ensued soon after the onset of the operation. Immediate exposure of the site of fistula revealed a cyanotic and feebly beating heart. Occlusion of the fistula emptying into the main pulmonary artery by means of a serrated clamp produced a dramatic improvement in cardiac activity. The electrocardiogram was usually monitored at the time of vessel ligation. In Gasul's fourth case,[28] myocardial ischemia occurred when the proximal end of the vessel was clamped, but "when the distal end was clamped, these changes were not noted." He emphasized a fundamental point. "The surgical correction should be aimed at closing the drainage area first before ligating the coronary artery proximal to the fistula." Neill[42] reported a 56-year-old patient with arteriosclerosis and hypertension who underwent ligation "of a dilated branch of the left coronary artery entering the conus of the right ventricle." Considerable diffuse tortuosity and sclerosis of the whole coronary tree was noted. She did not maintain the initial improvement following operation and persistent failure recurred.

TABLE VI. REPORTED SURGICAL CASES

COMPLICATIONS OF OPERATION	
No complications	15
Unspecified	3
Bradycardia, hypotension (preligation)	1
Pericarditis	3
ST↑ and T changes	3
ST↓ and T changes (transient)	1
Acute myocardial infarction	1
Stormy postoperative course	1
Death	1

To date, there has been only one instance of death following operation. This was a 32-month-old child with significant pulmonary hypertension, reported by Bosher.[11] The patient had marked cardiac hypertrophy with a very large pulmonary artery. At operation a large patent ductus was found and the pressures in the aorta and pulmonary artery were identical at 76/40 mm. Hg prior to occlusion of the ductus. After the ductus was clamped, the aortic pressure was 84/60 and the pulmonary artery pressure 58/28 mm. Hg. An additional abnormality was then discovered consisting of an aberrant branch of the left coronary artery draining into the right atrium. The electrocardiogram, which had showed a right ventricular strain pattern before the operation, showed no change following ligation of this vessel. The patient died rather suddenly 30 hours after operation, apparently with an arrhythmia. Postmortem examination showed marked congestion of the lungs. It was considered that death was the result of pulmonary hypertension.

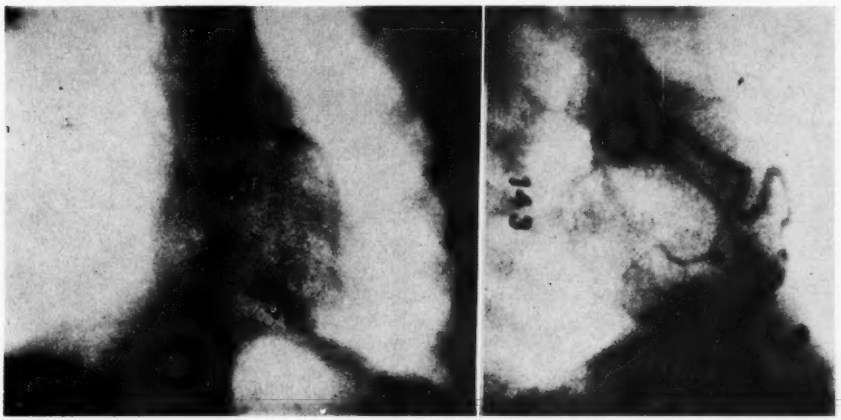

Fig. 1.—Case 1. A retrograde aortogram which shows the fistulous communication between both coronary arteries and the surface of the right ventricle.

CASE REPORTS

CASE 1.—G. McE., a 5-year-old white boy, was first seen Dec. 6, 1960. A murmur had been present since the age of 18 months. Easy fatigability and rapid heart action on mild exertion had been noted. Blood pressure in the upper extremities was 105/60 and in the lower extremities 115/60 mm. Hg. A high-pitched, loud, continuous murmur was heard diffusely over the left lower chest and was loudest in the fourth intercostal space near the apex. The phonocardiogram showed the predominant component of the murmur at the point of maximal intensity to be systolic in timing. The electrocardiogram was normal for the patient's age. Cardiac catheterization showed no striking abnormal findings. A borderline oxygen step-up at the right ventricular level was mentioned, and this was maintained in the pulmonary artery. A slight increase in pulmonary flow to one and two tenths times that of systemic flow was suggested. A retrograde cineaortogram (Fig. 1) showed enlarged branches of both the right and the left anterior descending coronary arteries entering a vascular plexus over the inferior portion of the right ventricle and appearing to empty into this chamber. Roentgenograms of the heart were normal. This patient was without symptoms, and further observation is planned.

CASE 2.—R. A. H., a 12-year-old white girl, was first seen July 7, 1953, for some increased fatigability on exertion but without limitation of activity. A murmur had been noted since the age of 3 months. From the age of 3 until the age of 12, there had been recurrent episodes of fever suspected of being rheumatic fever. Physical examination revealed a well-developed child with a faint systolic thrill over the second intercostal space, and a Grade 3 continuous machinery murmur most intense just under the sternum, or possibly to the right of the sternum, in the second intercostal space. Electrocardiographic studies were normal for the patient's age. Fluoroscopic and roentgenographic studies revealed mild increased prominence of the pulmonary artery (Fig. 2). Marked hilar pulsations were noted. A presumptive diagnosis of patent ductus was made and, on Sept. 2, 1953, the patient underwent exploratory thoracotomy. Detailed dissection revealed a very small patent ductus which was treated at that time by circumferential purse-string suture at both ends and multiple interrupted mattress sutures centrally. The thrill persisted, and the

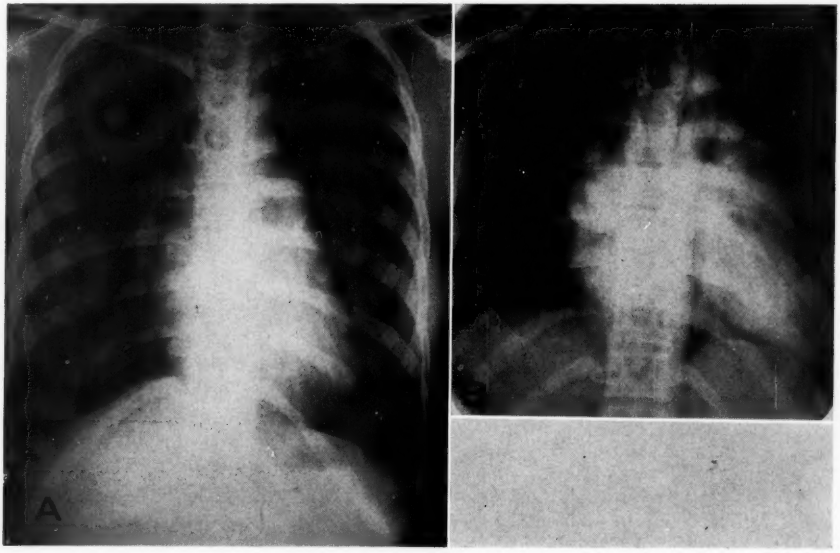

Fig. 2.—Case 2. *A*, Roentgenogram taken before first operation in 1953, is normal except for some prominence of the pulmonary artery. *B*, A venous angiogram made in June, 1954, which shows reopacification of the right atrium.

pericardium was opened and explored. No significant abnormality on the anterior surface of the heart was noted. The point of maximal thrill was noted at the junction of the posterior surface of the right atrium and the anterior surface of the right pulmonary artery in its portion within the pericardium. An arteriovenous fistula was suspected, which we were in no position to correct. Careful examination of the area between the main pulmonary artery and the aorta satisfactorily ruled out the possibility of an aortic septal defect or aorticopulmonary window. The postoperative course was complicated by pericarditis and pleural effusion, but prompt recovery occurred. On June 9, 1954, the patient was re-admitted for venous angiography. This revealed an anomalous vessel which was thought to arise from the aorta and to terminate in the right side of the heart. These studies were limited in that they were done in a single plane and through the venous route.

In March, 1960, failure to gain weight and easy fatigability were noted. The most disturbing symptom was upper substernal pressure radiating to the neck which accompanied vigorous exertion. Tachycardia was also noted at this time. More recently she had become

breathless on mild exertion. A continuous murmur was audible over the entire right chest and at the base of the heart anteriorly. The pulmonic component of the second sound was accentuated. The electrocardiogram was still considered to be normal. Cardiac catheterization was done on June 3, 1960, and the findings are summarized in Table VII. It was thought that there was a left-to-right shunt into the upper portion of the right atrium. The pulmonary flow was estimated to be one and three tenths times the systemic flow.

TABLE VII. RESULTS OF RIGHT HEART CATHETERIZATION (CASE 2)

	PRESSURE (MM. Hg)	O_2 CONTENT C.C./100 C.C.
Right Ventricle		
inflow	23/5	13.90
outflow	21/5	13.88
Pulmonary Artery		
main	21/10	13.91
right	18/7 (11)	14.13
Pulmonary Artery Wedge	M = 7.5	
Systemic Artery		
left radial	89/49 (68)	16.97
Superior Vena Cava		
high		13.20
low		13.54
Right Atrium		
high		15.10
mid	M = 2	14.40
low		13.82

Note the significant increase in oxygen content in the high right atrial sample.

Radiologic studies revealed slight cardiac enlargement, prominence of the main pulmonary artery and questionable enlargement of the right atrium, right ventricle, and left ventricle since the initial studies in 1953 (Fig. 3). A retrograde aortogram revealed a large tortuous vessel passing from the origin of the left coronary artery into the upper portion of the right atrium.

On July 25, 1960, a left lateral thoracotomy was performed. Numerous adhesions, both in the pleural and pericardial space, were encountered. The pericardium was widely opened and the area of maximal thrill was found to lie between the posterolateral surfaces of the main pulmonary artery and the left atrium. To obtain optimal exposure of this area, the ligament of the left superior vena cava, also known as the "vestigial fold of Marshall," was carefully transected. This ligament is situated between the left pulmonary artery and the undersurface of the right pulmonary artery and extends down to the left superior pulmonary vein and the surface of the atrium. It has been well described by Gray[64] and Buchanan.[65] It is formed by the folding of the serous layer of the pericardium over the remnant of the left duct of Cuvier. Its division allows considerably improved access to the posterior surface of the heart in this region (Fig. 4). The operation had been planned so as to use the pump-oxygenator and obtain hypothermic arrest if desired. As the dissection progressed, it was apparent this would not be necessary.

The left coronary pulmonary artery was identified, and found to be approximately four times the normal diameter. About 2 cm. above its normal point of branching a fistulous communication to an anomalously located coronary sinus was revealed. Distal to this communication the left common coronary artery abruptly diminished to normal diameter, and the left anterior descending and circumflex branches were decreased in size. The anomalous communication between the left common coronary artery and the coronary sinus measured 8 mm. in diameter. With considerable caution, the epicardium over these areas was incised.

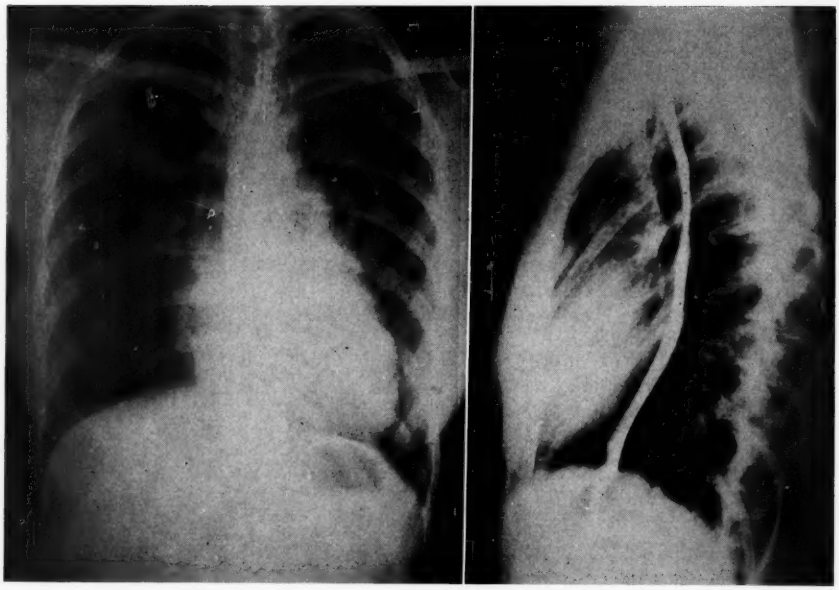

Fig. 3.—Case 2. Roentgenograms made in 1960 show progressive cardiac enlargement.

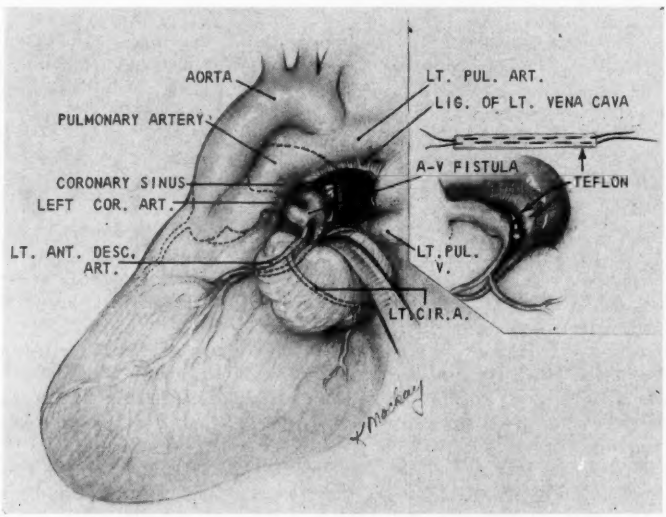

Fig. 4.—Drawings of the operative findings in Case 2 which show a fistulous communication between the left main coronary artery and coronary sinus. The exposure behind the main pulmonary artery was facilitated by excision of the ligament of the left vena cava.

The isolation of the fistulous tract was greatly facilitated by the use of the Beck ball-point dissector (Fig. 5), devised particularly for dissections about the coronary sinus in order to place circumferential ligatures in the Beck I operation. The extreme thinness of the aneurysmal wall of both the artery and coronary sinus suggested the possibility of ligatures cutting through. Accordingly, the fistula was ligated by a Teflon band followed by multiple transfixion sutures. The thrill was controlled completely and a significant decrease in the size of the coronary sinus was noted. An increase in pulsation of the left common coronary artery and its branches distal to the communication was also noted. Continuous electrocardiographic monitoring was carried out throughout the operation and no significant change was noted. The patient's postoperative course was uneventful except for episodes of pleural and pericardial pain of transient nature. For a few weeks following operation, steroids were administered because of this pericardial discomfort. By Sept. 2, 1960, no further pain was experienced. Examination revealed no murmur; this was confirmed by phonocardiogram. The heart was normal in size and the pulmonary vascular bed appeared normal on fluoroscopy.

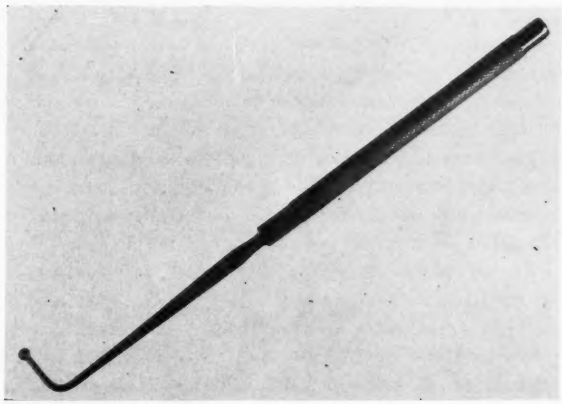

Fig. 5.—Beck ball-point dissector—a valuable instrument for placement of circumferential ligatures about coronary vessels.

SUMMARY AND CONCLUSIONS

Data on 73 patients with coronary arteriovenous fistulas or coronary arteriosystemic fistulas, and on one patient with a traumatic coronary arteriovenous fistula, have been presented. Most of the fistulas drained into the right ventricle, the coronary sinus and its tributaries, or the right atrium. In nine instances the drainage was directly into the pulmonary artery.

Diagnosis is difficult, the lesion being most commonly confused with patent ductus arteriosus. Retrograde angiography, using the biplane Elema apparatus or cineangiography, is indicated in any patient presenting a continuous murmur in whom the area of maximal intensity is elsewhere than in the left upper parasternal region.

The frequency with which the diastolic component of the continuous murmur in coronary arteriovenous fistula predominates over the systolic component is an important finding. Phonocardiographic study of all precordial continuous murmurs is recommended. Intracardiac phonocardiography can be quite helpful.

Twenty-seven patients have been operated upon. In thirteen instances the right coronary and in fourteen instances the left coronary, or an aberrant branch of this vessel, were involved.

In the earlier cases, ligation of the coronary artery was employed; more recently attempts to obliterate the fistula itself were made. In eight instances an aberrant vessel was ligated, which could well be considered the ideal operation for this lesion. Ligation of the fistula alone has been performed only on three occasions. When confronted with an aneurysmal enlargement of the feeding coronary artery, the choice lies between a transaneurysmal ligation of the nutrient coronary artery just as it enters the aneurysmal component, or the use of endoaneurysmorrhaphy. Immediate angiographic studies to ensure the patency and usefulness of the area of the vessel preserved may be necessary.

Two additional cases are presented. In one case the aneurysmal component is fed by both the left anterior descending coronary artery and the right coronary artery. The minimal degree of shunt, the normal heart size, and the absence of symptoms have indicated a period of observation in this patient. In the second patient, a fistula between the left common coronary artery and the coronary sinus was corrected by obliteration of the fistula alone. A unique feature of this case was the presenting symptom of angina pectoris.

In planning the operation for this lesion, it is desirable first to determine, if possible, the exact site of the fistula. A fistulous tract which is readily accessible and does not require the sacrifice of a major coronary artery might well be subjected to operation in the absence of any symptoms or of major disturbances in cardiac size or function. Any patient with angina, progressive cardiac enlargement, or incipient cardiac failure, is a candidate for operation.

In the cases of unusually difficult sites for correction, a pump-oxygenator with hypothermic arrest should be available for use if necessary.

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(For Discussion, see page 702.)

MITRAL REPLACEMENT: THE SHIELDED BALL VALVE PROSTHESIS

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PREVIOUS work in this laboratory has demonstrated that a ball valve will function as a hydraulically satisfactory prosthesis in the canine mitral orifice. Long-term survival continuing at 13 months following implantation has been obtained.[9, 10] The prosthesis which has evolved from this work has been used clinically, and experience with the first 8 patients operated upon from August, 1960, to March, 1961, has been reported elsewhere.[11] Clotting has thus far not been a clinical problem. In the dog, however, thrombotic occlusion of the prosthesis or hemorrhage from anticoagulant therapy to prevent this complication was found to interfere with further in vivo laboratory testing so that modification of the prosthesis for continued experimental use was necessary.

The present study was undertaken to determine the effect of exclusion of the suture line at the zone of fixation on the incidence of thrombotic occlusion of the valve and to report the results in terms of left atrial pressure studies, duration of survival, cardiac catheterization, and angiocardiography.

MATERIALS AND METHODS

Excision and replacement of the mitral valve with a ball valve prosthesis was carried out on 35 adult mongrel dogs using cardiopulmonary bypass and hypothermia to 28° C. The unshielded prosthesis (Fig. 1, *A*) was used in 9 dogs (*Group A*). The cage is of Lucite, the ball of heat-cured medical grade silicone rubber, and fixation is achieved by means of a margin of knitted Teflon cloth which is firmly anchored to the body of the prosthesis by a stainless steel ring and steel wire. The shielded valve shown in Fig. 1, *B* was used in 26 dogs (*Group B*). The two valves are identical in internal dimensions, such as area of inflow lumen, diameter, and excursion of the ball. The use of stainless steel for the cage of the shielded valve allowed reduction in external dimensions of the prosthesis without loss of strength. The shield is of silicone rubber and is retracted from the Teflon margin during insertion by means of a shield retractor (Fig. 1, *C*). The prosthesis is fixed to the mitral annulus by sixteen to twenty 3-0 silk sutures placed through the mitral annulus and then through the Teflon cloth margin. After removal of the shield retractor, the shield snaps into place, covering the atrial side of the suture line and surrounding zone of injured endocardium.

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The operation in all but the last two experiments was performed through the right chest with cannulation of the right carotid artery for arterial inflow and the azygous vein and right atrial appendage for caval drainage. Arterial and venous pressures, electrocardiogram, and left atrial pressures were monitored on a multichannel recorder. The left atrium was entered across the atrial septum with the heart slowed by hypothermia, and resection and replacement of the mitral valve was possible with 60 to 70 minutes of perfusion time. A more direct approach through the left chest was used in later experiments because the increased bulk of the shielded prosthesis and associated retractor mechanism made the transseptal approach awkward.

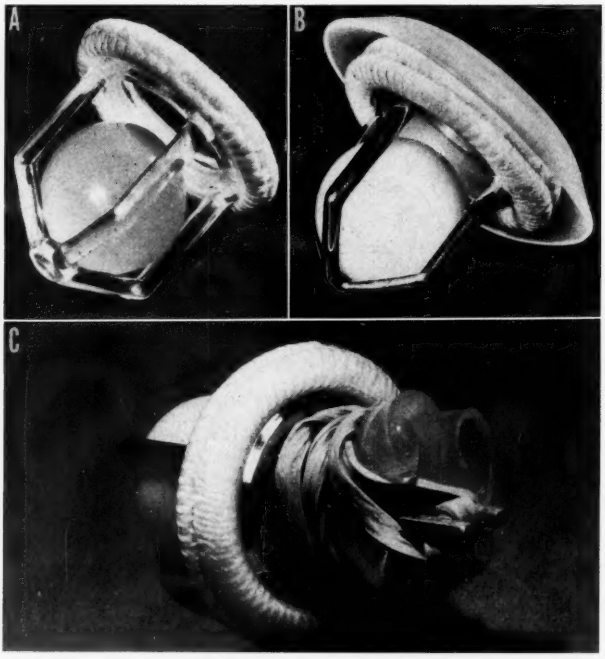

Fig. 1.—The ball valve mitral prosthesis for dog implantation. *A*, The unshielded valve. *B*, The shielded valve. *C*, The shielded valve with shield retractor in place. The silicone rubber ball of the shielded valve is barium impregnated.

All dogs were given one million units of penicillin daily for the first postoperative week. Dogs in *Group A* were given Depoheparin, 200 mg. twice daily, beginning on the third postoperative day and this was maintained until control with a long acting oral anticoagulant was established. Dogs in *Group B* were given no anticoagulant medication at any time in their postoperative course.

Angiocardiography, cineangiocardiography, right heart catheterization, and Cardiogreen dye studies were performed on all long-term survivors.

RESULTS

The results of mitral resection and ball valve replacement are summarized in Table I and Table II. Left atrial pressures measured by needle puncture immediately following insertion of the prosthesis in most dogs fell within

normal limits in both groups. A representative pressure tracing is shown in Fig. 2. In no instance was there evidence of thrombotic material on the left ventricular aspect of the prosthesis or on the silicone rubber ball.

Group A: The Unshielded Ball Valve.—As noted in Table I there were nine satisfactory insertions in nine experiments. One dog died on the first postoperative day and another on the third postoperative day with no cause of death able to be determined at autopsy. A small amount of thrombus material was noted at the suture line in these animals but did not extend on the prosthesis proper. Three dogs that died of hemothorax at 5 days and 1 at 8 days, due to anticoagulant therapy, demonstrated clot on the atrial side of the prosthesis covering the Teflon cloth and extending on to the inlet face of the cage but not interfering with valve function in any way (Fig.

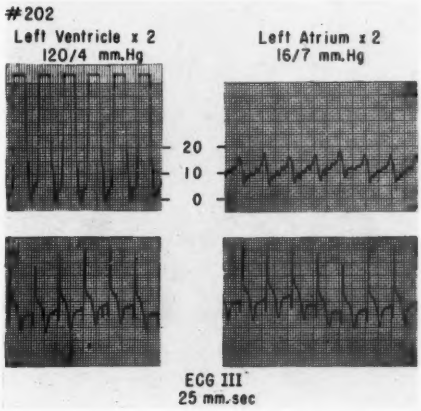

Fig. 2.—This figure shows simultaneous left atrial and left ventricular pressure tracings made immediately after mitral replacement with the shielded ball valve.

TABLE I. THE UNSHIELDED BALL VALVE (GROUP A)

DOG NO.	DURATION SURVIVAL (DAYS)	LEFT ATRIAL PRESSURES (MM. Hg) PRE-	POST-	ANTI-COAGULANT THERAPY	COMMENTS
158	385	—	11/8	Yes	Alive and in good health
160	17	5	15/11	Yes	Death due to acute thrombotic occlusion
161	5	5/1	7	Yes	Death due to hemothorax related to early anticoagulation; extensive clotting on atrial side of prosthesis
162	3	0	9	No	Death from undetermined cause
163	5	5	15/8	Yes	Death due to hemothorax related to early anticoagulation; extensive clotting noted on atrial side of prosthesis
165	5	5/0	4/2	Yes	Death due to hemothorax related to early anticoagulation; extensive clotting noted on atrial side of prosthesis
166	1	—	7/0	No	Death from undetermined cause
167	10	—	24/9	Yes	Death due to thrombotic occlusion
168	8	5/0	7/5	Yes	Death due to hemothorax related to early anticoagulation; extensive clotting noted on atrial side of prosthesis

3, *A*). Two dogs died of total occlusion of the prosthesis on the tenth and seventeenth day despite anticoagulant treatment (Fig. 3, *B*). One dog is still alive 13 months following implantation and in excellent health.

Group B: The Shielded Ball Valve.—In 26 operations, 8 dogs died during or soon after cardiopulmonary bypass due to technical errors of insertion related to the bulk of the shield and shield retractor. The results of eighteen satisfactory operations are shown in Table II. Left atrial pressures following insertion were similar to those in *Group A*. Results in terms of thrombosis of the prosthesis were strikingly dissimilar from *Group A*. Six dogs that died during the first week, 2 dogs during the second week, and one in the third

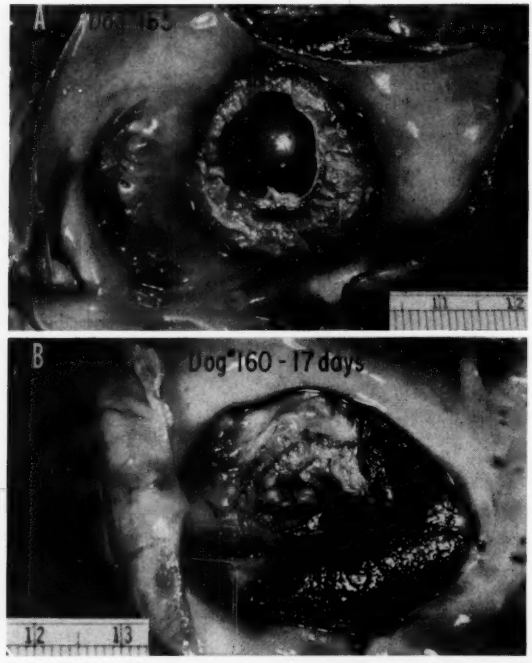

Fig. 3.—Postoperative left atrial view of the unshielded ball valve. *A*, Thrombus extends onto the Teflon cloth and Lucite rim of the cage from the suture line. The incision in the atrial septum is free of thrombus. *B*, Total occlusion of the unshielded valve by massive thrombus.

week showed no thrombosis on any external surface of the prosthesis (Fig. 4). The earliest thrombotic complication resulted in death at 21 days from renal infarction and, at postmortem examination of this dog, the valve was free of clot. One dog died of thrombotic occlusion of the valve at 24 days after implantation. In a dog dying at 23 days of partial dislocation, no thrombus was found on the prosthesis. Two dogs sacrificed at 64 and 180 days after insertion showed thrombus material extending out from under the shield along one margin of the prosthesis but in no way interfering with valve function (Fig. 5, *A*). An embolus to the bowel caused the death of one dog at 38 days

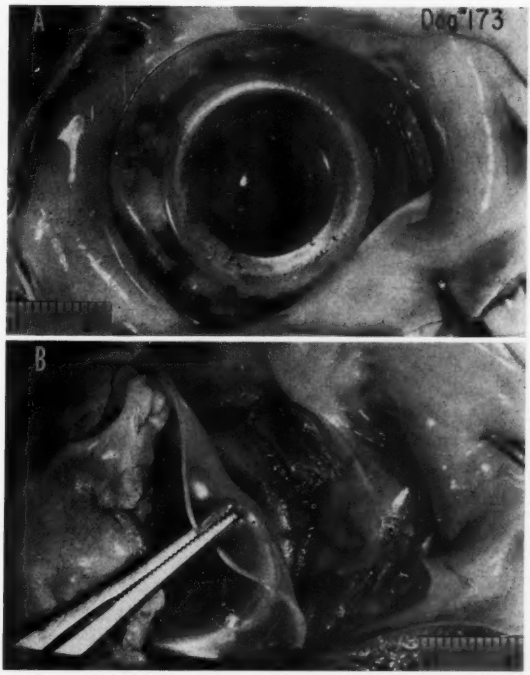

Fig. 4.—Postoperative view of the left atrial aspect of the shielded ball valve. *A*, There is no thrombus material on the external surface of the prosthesis. *B*, With the shield retracted, thrombus is seen at the zone of fixation and is totally contained by the shield.

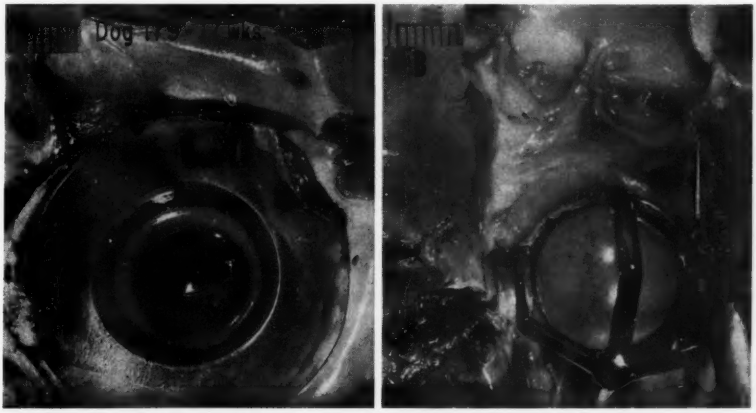

Fig. 5.—*A*, Late postoperative left atrial view of the shielded prosthesis showing only minimal clot along one margin of the shield. *B*, The left ventricular aspect of the valve in this dog demonstrates firm healing with endothelization of the Teflon cloth.

and in another at 122 days; these dogs showed a small amount of clot around the margin of the silicone rubber shield. One dog was successfully operated upon for saddle embolus at 28 days but was sacrificed at 64 days because of a protracted febrile illness shown at autopsy to be streptococcal endocarditis of the aortic valve. Thus, in *Group B* which received no anticoagulant treatment, thrombotic complications occurred in 6 of 12 dogs surviving beyond one week but in only one instance was there interference with valve function by the thrombotic process.

TABLE II. THE SHIELDED BALL VALVE (GROUP B)*

DOG NO.	DURATION SURVIVAL (DAYS)	LEFT ATRIAL PRESSURE PRE-	LEFT ATRIAL PRESSURE POST-	COMMENTS
173	5	5/0	12/5	Death due to partial dislocation; no clot on valve
174	15	2/0	7/2	Death due to partial dislocation; no clot on valve
176	180	--	--	Sacrificed because of endocarditis occurring after cardiac catheterization and angiocardiogram; no clot on ventricular side of prosthesis; small clot on periphery of Silastic shield
177	3	10/2	12/2	Death due to over-transfusion; no clot on valve
178	6	7/2	7/2	Death due to hemothorax; no clot on valve
179	122	3/0	8/3	Death due to small bowel infarction 2 weeks following cardiac catheterization and angiocardiography; no clot on ventricular aspect of prosthesis; small clot on periphery of silastic shield
180	21	3	5	Death due to renal infarction; no clot on valve; dog inactive because of wound disruption
181	46	3/0	10	Sacrificed because of chronic congestive failure due to partial dislocation with 5 mm. regurgitant orifice; no clot on prosthesis
182	23	7/4	20/10	Death due to massive dislocation; no clot on prosthesis
184	38	7	10/3	Death due to small bowel embolus; small clot along margin of shield
189	1	7/0	14/2	Death due to unknown cause; no clot on valve
190	9	--	15/5	Death due to unknown cause; no clot on valve
191	11	5/0	7/0	Sacrificed because of extreme weakness; no clot on valve; slight mitral insufficiency due to tearing out of two sutures
194	1	4/0	9/5	Death due to unknown cause; no clot on valve
195	2	2/0	7/0	Death due to unknown cause; partial dislocation
197	64	--	--	Sacrificed because of endocarditis; saddle embolus successfully removed one week following angiocardiogram; no clot on ventricular side of valve; small amount of clot at periphery of Silastic shield
199	24	12/5	17/9	Death due to thrombotic occlusion
202	14	18/8	15/5	Still alive

*No anticoagulant therapy.

Partial dislocation accounted for six early deaths with the shielded valve possibly due to technical difficulties encountered in inserting this prosthesis through the small left atrium of the dog. This complication was not found with the unshielded valve. In both groups, however, firm and lasting fixation was demonstrated. By the end of 2 weeks, fibroplasia along the margins of the mitral annulus anchors the prosthesis with sufficient force so that at autopsy the valve cannot be manually dislocated. At 3 weeks following implantation, fibrous ingrowth is apparent and by 6 weeks the cloth is endothelized and healed into place (Fig. 5, *B*).

There was no clinical evidence in surviving dogs of chronic cardiac disability except for Dog 181 who had congestive failure due to partial dislocation of the prosthesis. Generalized cardiomegaly or left atrial enlargement was not found on fluoroscopy or angiocardiography (Fig. 6). Angiocardiography of the long-term survivors in *Group B* with stainless steel valves showed no evidence of impingement of the case on the left ventricular outflow tract or on the ventricular endocardiocardium (Fig. 7). In some dogs, barium-impregnated silicone rubber balls were used in valve fabrication and periodic

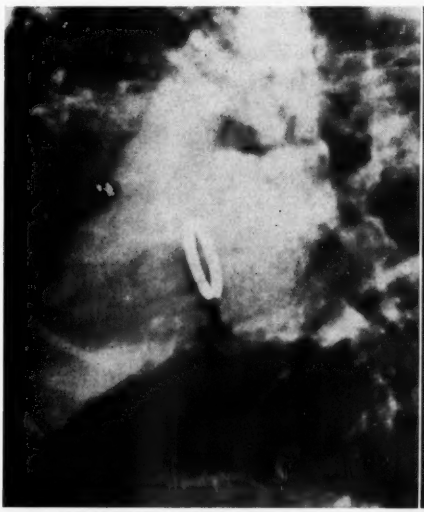

Fig. 6

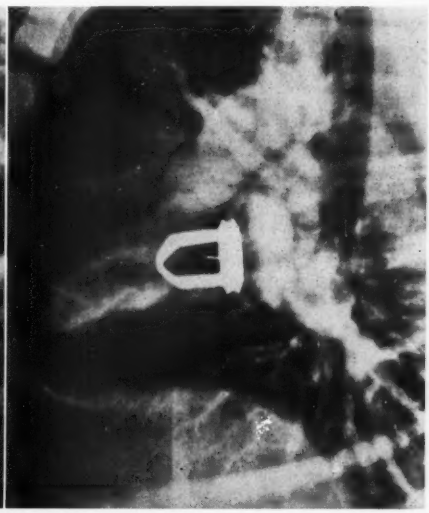

Fig. 7

Fig. 6.—Angiocardiogram with peripheral venous injection of contrast agent made one year after mitral replacement with the unshielded Lucite ball valve with radiolucent silicone rubber ball. There are no filling defects suggesting thrombus formation, and left atrial and ventricular size are normal.

Fig. 7.—Angiocardiogram of Dog 176 made 3½ months after valve replacement. At the instant of exposure the ball was moving at a velocity of 18.75 cm. per second (summed image double pulse exposure study). Note steel cross pins in radiolucent ball.

fluoroscopy disclosed full excursion of the ball with each cardiac cycle. Stainless steel pins were inserted into the radiolucent ball in 2 dogs and fluoroscopy and cinecardiography disclosed random spinning of the ball, thereby insuring even wear of the silicone rubber.

Cardiac output, electrocardiogram, and Cardio-green dye studies were normal under conditions of light pentothal anesthesia in the group of long-term survivors as shown in Fig. 8.

DISCUSSION

Mitral prostheses of varied materials and design have been demonstrated to function satisfactorily in the dog.[2, 4, 6, 8, 12, 13] However the common occurrence of thrombotic occlusion has frustrated attempts to gain long-term survival data with most prostheses. Experience gained from previous studies in this

laboratory, involving a wide variety of rigid prostheses and the results of the present study using the unshielded ball valve, has provided adequate autopsy material with which to study the gross pathology of such thrombus material in various stages of its development. Thrombosis appears first on the atrial aspects of the zone of fixation to the mitral annulus and then grows over the prosthesis by direct extension rather than multicentric formation. It reaches the valve inlet by 2 to 3 days after implantation and extends onto any leaflet mechanism attached to the annulus, causing occlusion within a few days following insertion. Occlusion of the ball valve occurs more slowly since thrombus must build up around the margin of the inlet into a bulky mass that gradually encroaches upon the lumen. The use of anticoagulant therapy prevented this final phase of the thrombotic process in only one

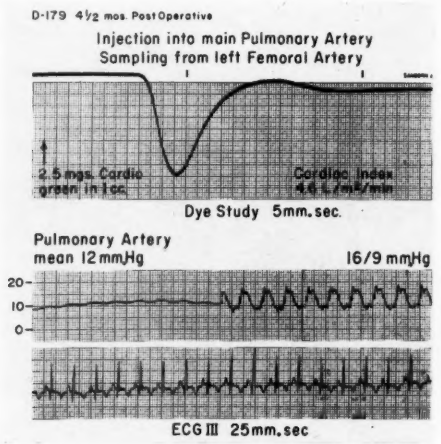

Fig. 8.—After mitral replacement with shielded ball valve, cardiac catheterization under light Penotothal anesthesia discloses normal pulmonary artery pressures and electrocardiogram. The dye study showing normal output and recirculation curve confirm clinical findings in this dog of normal cardiodynamics.

dog in *Group A* with the unshielded valve. The effectiveness of the shield in preventing massive occlusion of the ball valve supports the impression that clot develops in response to damaged endothelium at the suture line and, in this sense, is unrelated to the type of prothesis implanted. By excluding this area from the left atrium, the growth of thrombus is greatly impeded. The occurrence of occasional embolic phenomenon even under these circumstances, however, suggests that the problem of clotting on the prosthesis of the dog is incompletely solved. It may well be that the addition of anticoagulant therapy to the dogs in *Group B* would be effective in reducing the incidence of emboli in this group.

Since embolic occlusion or embolization does not occur during the first few weeks after implantation of the shielded prosthesis, anticoagulant therapy may be given relatively late in the postoperative period, thereby avoiding the bleeding problems encountered with early anticoagulation.

There is now sufficient evidence from the work of other investigators,[1, 3, 5, 7] as well as our own experience, that the marked propensity of the dog to thrombotic occlusion or massive embolization from a mitral prosthesis is not shared by the human being. In a previous report from this clinic of 8 patients in whom mitral resection and replacement with the unshielded ball valve was performed, there were two operative deaths unrelated to the prosthesis, one late death due to bacterial endocarditis, and no complications related to thromboembolic disease. Three additional patients have subsequently been operated upon with a similar prosthesis with no deaths or complications. Oral anticoagulant therapy was started on the seventh postoperative day in these patients and has been maintained in the 8 surviving patients. The need for prolonged treatment with anticoagulant drugs is as yet undetermined. The occurrence of occasional thrombotic complications with the ball valve in the descending aorta of the human and the results of this study in the dog suggests that until further information is obtained it is prudent to maintain oral anticoagulant treatment for an indefinite period in patients who survive mitral resection and replacement.

The initial success of the unshielded valve in the human being does not decrease in importance the need for a mitral prosthesis allowing long-term survival in the dog. Clinical use of a mitral prosthesis must be limited at the present time to patients with far-advanced or otherwise uncorrectable mitral disease. Laboratory evaluation of a prosthesis does not know these limitations and can proceed on a large and well-controlled scale without artifact due to disease of other valves and myocardium. However, selection of a mitral prosthesis for initial clinical trial depends only in part on the results of in vivo testing in the normal dog. Of great importance is the ease with which a prosthesis lends itself to the surgical treatment of valvular disease. A great premium is to be placed on speed and ease of insertion by conventional approaches with minimal surgical trauma. The goal in this laboratory has been to develop a prosthesis the function of which is independent of a complex subvalvular mechanism, such as artificial chordae tendineae requiring adjustment in the operating room and surgery more extensive than simple suture to the mitral annulus. While the shielded as well as the unshielded valve satisfy these criteria, the added simplicity of the unshielded valve led to its initial clinical trial despite the clotting problem it provided in the dog.

SUMMARY

A mitral prosthesis has been described that allows satisfactory hydraulic function, firm fixation, and long-term survival in the dog. While clinical experience with this prosthesis in 11 patients thus far operated upon has been satisfactory with no deaths or complications from thromboembolic disease, thrombotic occlusion of the prosthesis or hemorrhage from postoperative anticoagulant therapy to prevent this complication was found to interfere with further laboratory testing in the dog. A modification of the ball valve

which provides for exclusion from the circulation of the atrial side of the suture line by means of a retractable Silastic shield has resulted in a marked diminution of clot formation on the prosthesis and prolonged survival in the dog without anticoagulant treatment. Late angiocardiography and cardiac catheterization studies provide evidence of satisfactory long-term function of the ball valve prosthesis.

Species differences have therefore led to the use in this clinic of an unshielded ball valve for human mitral replacement and a shielded ball valve as the prosthesis of choice for further testing in the dog.

The authors express their appreciation to Silas Braley, of Dow-Corning, for his help in supplying silicone rubber and other silicone products used in the fabrication of the prosthesis, to Norman Jeckel, of U. S. Catheter and Instrument Company, for making available various Teflon cloth products used in the fixation ring, and to R. R. Miller, of Precision Metalsmiths Incorporated, Cleveland, Ohio, for his help with metallurgical problems involving casting techniques. The prostheses used in the present study were obtained from the Edwards Laboratories, Incorporated, 603-H Alton Street, Santa Ana, California.

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(For Discussion, see page 702.)

PROLONGED SURVIVAL AFTER TOTAL REPLACEMENT OF THE MITRAL VALVE IN DOGS

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A SATISFACTORY mitral valve prosthesis for clinical use is clearly needed. In clinical experience prosthetic replacement of the mitral valve has been considerably less successful[1-4] than similar procedures carried out on the aortic valve.[5-8]

Experimental work on replacement of the mitral valve not only by us[9, 10] but also by others[11-14] has been hampered by failure to achieve long-term survival, because of thrombotic complications. Work previously reported from this laboratory by Frater and one of us[10] dealt with a group of 23 dogs that had replacement of the mitral valve with a monocusp valve. Nineteen of these animals (83 per cent) died of thrombosis. The average survival period was 12 days for the entire group and 9 days for the group of 19 dogs that died of thrombosis.

The present study was undertaken in an effort to achieve survival of more than a week or two by minimizing clotting. This study differed from the previous one in the following ways: (1) changes in the technique of inserting the prosthesis, (2) use of open-cell polyurethane foam to cover the surfaces of the prosthesis, and (3) use of Dicumarol as an anticoagulant.

MATERIAL AND METHODS

Forty-two healthy adult mongrel dogs, varying in weight from 9 to 19.2 kilograms, were used. The operation was performed with the animals under general anesthesia induced by the intravenous administration of sodium pentobarbital, 25 mg. per kilogram of body weight. A monocusp prosthesis made of Mylar,† similar to the one previously reported from this institution, was used throughout this study.

Construction of Prosthesis.—The valve consisted of two parts: a cusp and a rigid ring.[10] The ring was made of five strips of Mylar (Fig. 1). Each was 0.19 mm. thick

From the Mayo Clinic and Mayo Foundation; Rochester, Minn.

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**Section of Surgery.

†Mylar is a polyester film made by E. I. du Pont de Nemours & Co., Wilmington 98, Delaware.

(750-gauge Mylar), 3 mm. wide, and 5.5 to 7.1 cm. long, the length depending on the size and weight of the dog. A strip of Mylar resin* was placed between the strips of Mylar, and heat was applied to glue the strips together. The heat allowed molding of the ring into a straight and a curved segment. From the innermost strip of Mylar, a long, 1 mm. wide, rectangular portion was removed before the strips were glued together, in order to make a groove on the inner surface of the ring. After the ring was made, paired holes were drilled throughout the length of the ring within the groove just described. The number of paired holes varied between 7 and 14, depending on the size of the ring. A running suture of wire was passed in and out through these holes, and both ends of the suture were tied on the outer surface of the ring (Fig. 1, *a*). The small loops of wire on the inner surface of the ring

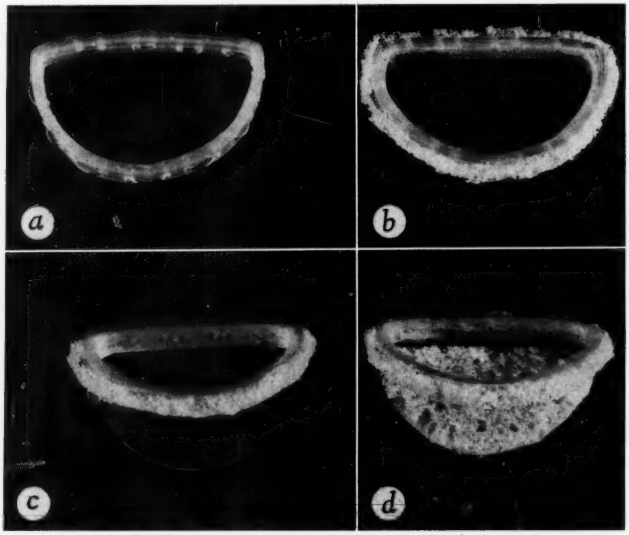

Fig. 1.—Construction of flexible monocusp Mylar prosthesis covered with polyurethane. *a*, Mylar ring with wire in place. *b*, Polyurethane layer has been cemented to outside of ring. Additional strip of Mylar was used to cover inner surface of ring, rendering it smooth. *c*, Mylar cusp attached to ring. *d*, Cusp covered with polyurethane.

were situated in the groove. Each loop formed by the running wire suture around the outside of the ring was used to secure an interrupted suture employed in anchoring the valve. The groove and the wire suture lying in it on the inner surface of the ring were covered with a sixth strip of 0.12 mm. thick Mylar (500-gauge Mylar), in order to make the inner surface smooth (Fig. 1, *b*).

The outer surface of the ring, together with the loops of wire, was covered with a thin layer of open-cell polyurethane† (Fig. 1, *b*). The cusps of some of the valves also were covered with polyurethane (Fig. 1, *c* and *d*). Mylar resin was used to cement the Mylar and polyurethane together.

Method of Insertion.—After overnight sterilization in aqueous benzalkonium chloride (Zephiran), the valve was prepared for insertion by threading long, interrupted 2-0 silk sutures through each loop of wire on the outer surface of the ring. The thorax of the animal was then entered through an incision in the left fourth or fifth intercostal space. The method of extracorporeal circulation employed was the same as that used in the previous study reported from this laboratory.

*Mylar resin (schjelbond 100), a heat-sealing adhesive for polyester film, is made by G. T. Schjeldahl Co., Northfield, Minnesota.

†Polyurethane (Stafoam PE102) is manufactured by the American Latex Products Corporation, Hawthorne, California.

The mitral valve was exposed through a left atriotomy, the incision extending from the tip of the appendage to the lower border of the left inferior pulmonary vein. After inducing ventricular fibrillation, the aorta and pulmonary artery were cross-clamped together. In the ischemic, fibrillating, bloodless heart, both cusps of the mitral valve with their chordae tendineae and papillary muscles were excised, leaving only a 2 mm. rim of valvular tissue attached to the annulus. The prosthesis was then positioned in such a way that the straight side of the ring corresponded to the attachment of the posterior cusp to the annulus. In this position the cusp closed toward the aorta. The prosthesis was then anchored to the annulus of the mitral valve with the interrupted silk sutures. The technique of insertion was such that the silk sutures and their knots were located beneath the thin strip of valvular tissue that was left attached to the annulus; it was hoped that this technique would help to minimize thrombus formation. Interrupted mattress sutures were used. After each suture was tied, the remaining flap of valve tissue covered not only the suture line and the knots but also the ring itself (Fig. 2).

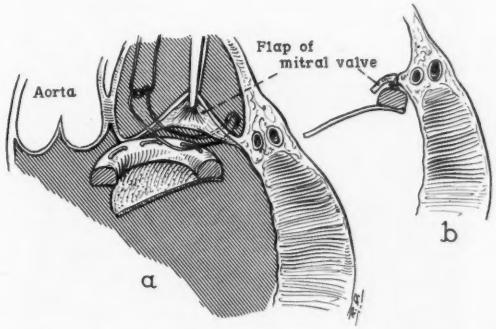

Fig. 2.—*a*, Technique of suturing valve to annulus. *b*, When sature is tied, silk suture and knot are situated beneath flap of valve tissue left attached to annulus.

Method of Anticoagulation.—Twenty dogs received Dicumarol as an anticoagulant after the operation. Although the dosage varied, the usual procedure was to give 25 mg. of Dicumarol the first day after operation, 12.5 mg. on the third day, and 12.5 mg. on the fifth day. This 5-day dosage regimen was repeated thereafter until the dog died or it was decided to stop administration of the drug.

RESULTS

Thirty-three of the 42 dogs that underwent replacement of the mitral valve survived more than 24 hours. Four of the 9 that did not survive more than 24 hours died on the operating table; 3 of these succumbed as a result of technical complications in the insertion of the valve, and the fourth dog died as a result of perfusion difficulties. In 3 of the 5 other animals that died during the first 24 hours after operation, the cause of death could not be definitely established; the fourth died from hemorrhage into the thoracic cavity and the fifth from mitral insufficiency that resulted when the sutures in the annulus failed to hold.

The 33 dogs that survived for periods longer than 24 hours can be classified into four groups on the basis of the type of valve used and of the use or

nonuse of anticoagulants. A flexible monocusp Mylar valve with a layer of polyurethane around the ring was used in all groups.

Group 1.—Polyurethane foam covered the surfaces of the cusp in this group, and Dicumarol was administered the day after operation. The anticoagulant therapy was continued for 2 to 8 weeks. There were 8 dogs in this group (Table I). Six of the 8 dogs survived more than a month, and one of these survived 10 months and 8 days. Death in this group was due to a variety of reasons, but clotting was encountered in three instances. Clots observed in this investigation were of two types: one was a massive thrombus that

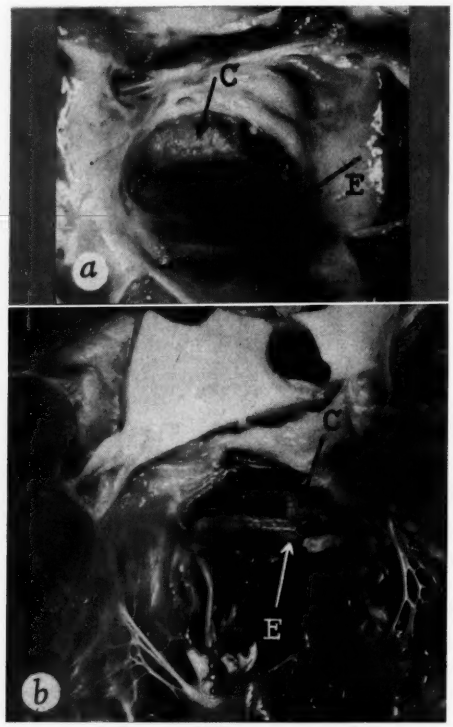

Fig. 3.—Appearance of polyurethane-covered Mylar valve 70 days after operation (dog 2 of Group 2). *C* = delayed form of clotting over cusp and beneath ring. *E* = smooth endocardium that has covered ring and advanced down to cover cusp. *a*, Left atrial view. Note that orifice of prosthesis is wide open. *b*, Left ventricular view. Note smooth layer of endocardium covering posterior surface of cusp.

occurred early in the postoperative period; it completely occluded the orifice of the prosthesis, and the dog died within a day or two, of pulmonary edema. The other type occurred over the cusp and along the inferior surface of the ring 1 to 2 months after the operation. The orifice of the prosthesis remained patent, and both the ring and the cusp of the valve were covered with smooth endocardium. The animal succumbed 1 to 2 weeks later from progressive heart failure due to mitral insufficiency; the insufficiency was caused by incomplete closure of the cusp against the ring (Fig. 3).

In Group 1, only one dog had early clotting with massive thrombosis at the orifice of the valve, while the delayed type of clotting developed in 2 other dogs.

Because of the relative lack of thrombosis in this group, particularly that of the early massive type seen commonly in our previous experiments, the same method was used to insert a flexible monocusp Mylar valve in other groups of dogs in an effort to elucidate the role played by the postoperative anticoagulant therapy, the use of polyurethane over the valvular cusp, and the size of the prosthesis.

Group 2.—Polyurethane foam covered the surfaces of the valvular cusp in this group, but anticoagulant therapy was not used. There were 9 dogs in this group (Table I). Although one dog survived more than 5 months, only 3 lived more than a month. Early clotting at the orifice of the prosthesis was the most common fatal complication in this group; it occurred in 4 dogs. The delayed type of clotting occurred in one animal 70 days after operation. The orifice of the prosthesis was patent, and both the ring and the cusp were covered with smooth endocardium (Fig. 3).

Group 3.—An uncovered valvular cusp was used in this group, and anticoagulant therapy was instituted postoperatively and continued through the survival period. There were 11 dogs in this group (Table I). Three of the 11 dogs survived more than a month, and one survived for 3 months. The most common cause of death in this group was a broken valvular hinge, which occurred in more than 50 per cent of the animals. In the previous two groups this complication occurred only four times among the 17 dogs that had covered cusps.

Group 4.—An uncovered valvular cusp was used in this group, but anticoagulant therapy was not used. There were 5 dogs in this group (Table I). No long-term survival was achieved. The two main causes of death were early massive clotting at the orifice of the prosthesis and a broken hinge, the former having been the most common cause of death in Group 2 and the latter that in Group 3. In other words, complications in this group were a combination of the main complications encountered in the previous two groups.

The data obtained in the four groups are summarized in Tables I and II.

PRESSURE STUDIES AND DYE-DILUTION CURVES*

Cardiac catheterization was performed in 3 dogs, at 37 days after operation in one, 67 days in another, and 112 days in the third. The valvular cusps in the first 2 dogs (dogs 3 and 8 of Group 3) were uncovered. The cusps of the third animal (dog 3 of Group 2) was covered with polyurethane. A thrill was palpable over the precordium of the second and third dogs.

With the animal under the effects of general anesthesia induced by the intravenous administration of sodium pentobarbital, the left ventricle was catheterized through the right femoral artery. The left atrium was catheterized by means of a modified Ross technique,[15] in which the catheter was introduced

*The physiologic studies were kindly performed by Dr. D. Donald.

TABLE I. RESULTS OF PROSTHETIC MITRAL VALVE REPLACEMENT IN DOGS

GROUP 1			GROUP 2			GROUP 3			GROUP 4		
DOG NUMBER	POST-OPERATIVE SURVIVAL (DAYS)	CAUSE OF DEATH	DOG NUMBER	POST-OPERATIVE SURVIVAL (DAYS)	CAUSE OF DEATH	DOG NUMBER	POST-OPERATIVE SURVIVAL (DAYS)	CAUSE OF DEATH	DOG NUMBER	POST-OPERATIVE SURVIVAL (DAYS)	CAUSE OF DEATH
1	154	Broken hinge	1	2	Cause unknown	1	9	Bleeding	1	15	Clot at orifice
2	4	Bleeding	2	70	Clot over cusp and under ring	2	11	Failure of sutures to hold	2	7	Clot at orifice
3	312	Broken hinge	3	157	Broken hinge	3	91	Broken hinge	3	7	Broken hinge
4	93	Failure of sutures to hold	4	58	Broken hinge	4	6	Bleeding	4	11	Broken hinge
5	32	Clot over cusp and under ring	5	15	Clot at orifice	5	13	Failure of sutures to hold	5	9	Broken hinge
6	60	Clot over cusp and under ring	6	10	Clot at orifice	6	7	Broken hinge			
7	35	Broken hinge	7	2	Cause unknown	7	3	Cause unknown			
8	17	Clot at orifice	8	7	Clot at orifice	8	39	Broken hinge			
			9	5	Clot at orifice	9	7	Broken hinge			
						10	81	Broken hinge			
						11	13	Broken hinge			

through the right external jugular vein into the right atrium and then pushed into the left atrium across the interatrial septum. The pressures recorded in these 3 animals are reproduced in Table III. Dog 8 of Group 3 had almost normal pressures; there was a small end diastolic gradient between the left atrium and left ventricle, suggesting minimal mitral stenosis (Fig. 4). This

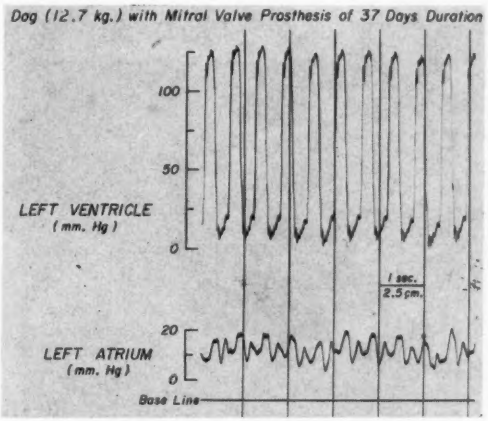

Fig. 4.—Simultaneous left ventricular and left atrial pressures 37 days after operation. Mean left atrial pressure was 11 mm. of mercury.

TABLE II. SURVIVAL PERIOD AND CAUSES OF DEATH AFTER PROSTHETIC MITRAL VALVE REPLACEMENT

	CUSP COVERED WITH POLYURETHANE		CUSP NOT COVERED		
	ANTICOAGULANTS USED	NO ANTICOAGULATION	ANTICOAGULANTS USED	NO ANTICOAGULATION	
	GROUP 1*	GROUP 2	GROUP 3	GROUP 4	TOTALS
Number of dogs	8	9	11	5	33
Average survival (days)	88	36	25	10	41
Cause of death					
Broken hinge	3	2	6	3	14
Clot at orifice	1	4	0	2	7
Clot over cusp and below ring	2	1	0	0	3
Bleeding	1	0	2	0	3
Failure of sutures in annulus to hold	1	0	2	0	3
Unknown	0	2	1	0	3

*One dog in this group is still alive 7½ months after operation.

TABLE III. POSTOPERATIVE PRESSURE STUDIES AFTER MITRAL VALVE REPLACEMENT

	BLOOD PRESSURE (MM. Hg)									
	LEFT VENTRICLE		RIGHT ATRIUM		RIGHT VENTRICLE		LEFT ATRIUM			LEFT A-V END DIASTOLIC GRADIENT
DOG NUMBER	SYST.	DIAST.	MAX.	MIN.	MAX.	MIN.	MAX.	MIN.	MEAN	
8 (Group 3)	130	12	5	−5	37	−3	22	3	11	4
3 (Group 3)	120	11	10	−5			40	10	27	1
3 (Group 2)	160	15	18	−1	80	0	55	15	37	5

animal died 2 days after catheterization, because of a broken hinge. The orifice of the prosthesis was wide open, and it was difficult to explain the residual end diastolic gradient.

Dog 3 of Group 3 and dog 3 of Group 2 had mitral regurgitation. These animals died 25 and 45 days after catheterization, respectively, because of a broken hinge. The mitral insufficiency was easily explained by the findings at the postmortem examination. In both dogs the prosthesis was detached from

Fig. 5.—Mitral opening in dog 3 of Group 3 seen through left atrium. Ring of prosthesis is detached from annulus at anterolateral commissural area. Mitral insufficiency was present.

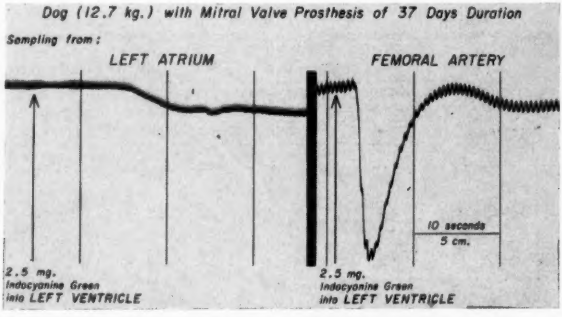
Dog (12.7 kg.) with Mitral Valve Prosthesis of 37 Days Duration
Sampling from:
LEFT ATRIUM
FEMORAL ARTERY
10 seconds
5 cm.
2.5 mg. Indocyanine Green into LEFT VENTRICLE
2.5 mg. Indocyanine Green into LEFT VENTRICLE

Fig. 6.—Dye-dilution curve in dog 8 of Group 3, 37 days after insertion of prosthesis. *Left panel,* Injection site was left ventricle. Blood was sampled from left atrium during injection. There was no early appearing dye, indicating absence of mitral insufficiency. A small quantity of dye appeared after 6.3 sec., representing recirculation of dye. *Right panel,* Injection site was left ventricle. Blood was sampled from right femoral artery. Appearance time was 1.1 sec.

the annulus at the anterolateral commissural area, so that regurgitation occurred outside the ring (Fig. 5). The orifice of both prostheses was wide open. The layer of polyurethane that covered the cusp of the valve inserted in dog 3 of Group 2 had not been invaded by fibrous tissue.

Dye-dilution curves were obtained in dog 8 of Group 3 and dog 3 of Group 2. Two cubic centimeters of indocyanine green (Cardio-green) was injected rapidly into the left ventricle through the left ventricular catheter and, during

the injection, samples of blood were obtained from the left atrium through the left atrial catheter. The dye curve for dog 8 of Group 3 was normal (Fig. 6); that for dog 3 of Group 2 was compatible with mitral regurgitation.

PATHOLOGIC CONDITIONS

Polyurethane was used in this study for two reasons. First, it was hoped, on the basis of the report by Braunwald and associates,[1] that clotting would be minimized by covering the surfaces of the prosthesis with polyurethane. Second, although Ivalon had proved satisfactory for purposes of fixation of the

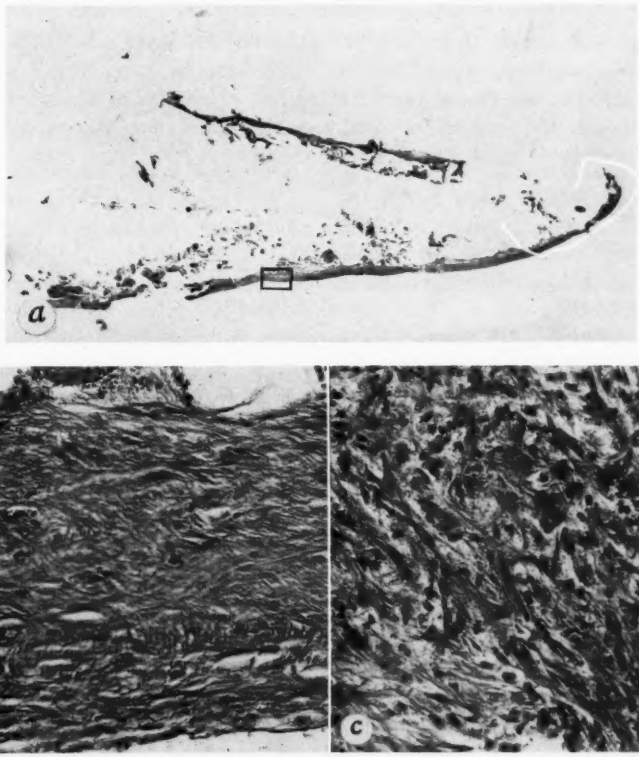

Fig. 7.—Photomicrograph of polyurethane-covered cusp in dog 2 of Group 2, 70 days after operation. Death was due to late secondary clotting. *a*, Cusp of valve. Black square indicates section reproduced in *b* (hematoxylin and eosin; ×5). *b*, Invasion of polyurethane with fibrous tissue has occurred (hematoxylin and eosin; ×200; reduced ⅙). *c*, Higher magnification of same area, showing cellular details (hematoxylin and eosin; ×285; reduced ⅙).

valve in our previous experiments,[9, 10] in one of our patients treated by prosthetic replacement of the mitral valve there was no ingrowth of host tissue into the Ivalon ring.[2] It was hoped that the use of polyurethane around the ring of the valve would offer a better framework for ingrowth of fibrous tissue and thus promote better fixation.

Polyurethane did not prevent clotting. Although massive thrombosis occluding the mitral orifice was found in only 7 of the 33 surviving dogs, 5 of these had polyurethane covering both surfaces of the valvular cusp. Moreover, the delayed form of clotting occurred only when polyurethane covered the cusp; this was observed in 3 dogs. Fibrous tissue was found invading the polyurethane of the cusp under certain conditions (Fig. 7). This reaction seemed to depend on whether or not anticoagulants were used. Thus, there was no ingrowth of fibrous tissue when anticoagulants were used for more than 5 weeks after operation, whereas there was demonstrable invasion of the polyurethane of the cusp by fibrous tissue when anticoagulants were used for lesser periods, or, with one exception, when they were not used at all.

Ingrowth of fibrous tissue into the polyurethane layer around the ring of the prosthesis also occurred. However, in 7 dogs the valve was found to be detached from the annulus of the mitral valve. This lack of healing seemed to be a function of the number of sutures used; it was not observed when more than 10 sutures were employed to anchor the valve.

COMMENT

Our goal of achieving prolonged survival after total replacement of the mitral valve of dogs with a prosthesis was partially realized. Twelve dogs, or 36 per cent of the group of 33 animals that lived beyond the first 24 hours after operation, survived for more than 1 month, whereas only one dog in our previous study survived for this length of time. Eight dogs lived 2 months or more after operation. Five animals were alive 3 or more months, and 3 survived for more than 5 months after operation. One dog lived as long as 10 months and 8 days (312 days) after operation.

When the dogs of Group 1 are considered, all but 2 lived beyond the first month. Reduction in the incidence of massive thrombosis over the mitral orifice was responsible for the prolonged survival of this group. When the other three groups were studied in an effort to elucidate the reasons for the low incidence of clotting observed in Group 1, it became apparent that several factors were responsible for this reduction, and it was difficult to define exactly the importance of each.

Method of Insertion.—Because of the tendency toward clotting at the point where the prosthesis is sutured to the mitral annulus, Starr[13] covered the entire suture line and the operative area with a retractable silicone rubber shield, and this seemed to help in reducing clotting. Previous experience in our laboratory suggested that covering of the suture line by natural valve tissue did not prevent clotting. However, the method of insertion used in the present study, which allowed retraction of all suture material and knots beneath the flap of valve tissue that was left attached to the annulus, seemed influential in preventing thrombosis. With the use of this technique, prolonged survival occurred even when anticoagulants were not used, and 3 dogs in Group 2 survived for 2 months or more and one for more than 5 months after operation.

Anticoagulation.—Although previous experience reported from this institution suggested that anticoagulation with heparin did not prevent clotting at the orifice of the prosthesis, results in the present study indicate that anticoagulant therapy with Dicumarol was important in reducing clotting. Comparing Groups 1 and 2, in which the same type of prosthesis was used, the average survival period in Group 1 was more than double that in Group 2. Anticoagulants were used in Group 1 and were not employed in Group 2. In Groups 3 and 4, in which the same type of valve was inserted, the average survival period was 2½ times more in Group 3 than in Group 4. The use of Dicumarol in Group 3 was the only difference between Group 3 and Group 4.

Only one dog of 20 that received adequate doses of Dicumarol died from massive clotting at the orifice of the prosthesis.

Size of Valve.—No clotting occurred in valves that had a ring larger than 6.2 cm. in inner circumference. Massive thrombosis at the orifice of the prosthesis occurred mostly with valves that had an inner circumference of 5.5 cm.

Use of Polyurethane.—Polyurethane did not contribute to the low incidence of clotting, as was previously noted. However, it was observed that when the cusp of the valve was covered by a thin layer of polyurethane, the Mylar hinge (which was not covered by polyurethane) remained intact for a much longer period than it did when the Mylar cusp was bare, even when no tissue had grown into the polyurethane covering the cusp.

Problem of the Hinge.—Frater thought that a flexible monocusp valve would protect the hinge from fracturing by distributing the movement of the cusp over several hinges. However, he could not test this theory because the great majority of his dogs died within the first 2 weeks after operation. In the present study, flexibility of the cusp did not relieve the stress imposed upon the hinge. Fourteen dogs of 33 that survived the first 24 hours after operation died because of fracture of the hinge. This fatal complication occurred as early as 7 days and as late as 312 days after operation. Either a defect in construction or fatigue of the Mylar at the hinge area, or both, could have contributed to this complication. It is because of this accident that the objective of this study was only partially achieved. Uncovered Mylar monocusp valves are clearly not suitable for clinical use. At present, Teflon fabric is being used to reinforce the hinge of the monocusp Mylar valve, and such a prosthesis is currently being tested.

Results of late physiologic studies in 3 dogs indicate that when firm healing occurs between the ring of the prosthesis and the annulus of the mitral valve, a flexible monocusp prosthesis made of Mylar can replace the natural mitral valve and maintain relatively normal hemodynamic conditions.

Ideal conditions would seem to prevail when good healing occurs between the ring of the prosthesis and the surrounding tissue and when there is ingrowth of tissue into the cells of the polyurethane covering the cusp. Such a situation would take advantage of the host tissues for strength and durability of the cusp as well as of the hinge; it would then not be necessary to depend

entirely on the material used in the construction of the hinge. From the data gathered it would seem that to reach such a goal anticoagulants should not be used during the first week or two after operation, so that fibrin may be allowed to become deposited over the cusp; subsequent ingrowth of tissue into the polyurethane and covering of the cusp by a thin endocardium-like tissue would thus be facilitated. Anticoagulant therapy should then be instituted to prevent the delayed form of clotting. It is thought that this type of thrombosis occurs as a result of traumatic ulceration caused by the beating of a covered cusp against the ring.

SUMMARY

The mitral valve of 42 healthy adult mongrel dogs was replaced with a flexible monocusp prosthesis made of Mylar. A thin layer of polyurethane was cemented to the outside of the cusp in some of the valves. A special technique of insertion was used that permitted covering of the suture line and the knots by valve tissue, leaving a smooth surface.

Of the 33 surviving dogs, 12 (36 per cent) lived more than a month. Five animals were alive 3 or more months, and 3 survived for more than 5 months. One dog lived 10 months and 8 days (312 days) after operation.

In only 7 of the 33 dogs did massive thrombosis at the orifice of the prosthesis occur. Although the use of Dicumarol seemed to minimize clotting, other factors that seemed of importance in this regard were the method of insertion and the size of the valve. The polyurethane per se did not contribute to the low incidence of thrombosis. Five of the 7 animals in which the massive clot at the orifice developed had a layer of polyurethane covering both surfaces of the cusp of the prosthesis.

Fracture of the hinge of the valve proved to be the most common complication in the present study; it occurred 14 times. All of the late deaths were due to this complication, which did not occur when the polyurethane covering the cusp had become invaded by host tissue.

Late physiologic studies performed in 3 dogs suggest that a flexible monocusp prosthesis made of Mylar can maintain relatively normal hemodynamics if good healing of the valvular ring occurs and if the hinge remains intact.

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(For Discussion, see page 702.)

TOTAL EXCISION OF THE MITRAL VALVE AND REPLACEMENT WITH THE AUTOLOGOUS PULMONIC VALVE

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Raymond C. Stofer, D.V.M. (by invitation), and
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THE ideal replacement for an irreparably damaged heart valve has thus far proved to be an elusive goal. Synthetic valves suffer the hazards of thrombus formation, material fatigue, and imperfect fixation. A valve of viable autologous tissue would seem to offer the greatest promise of success.

Evidence has been presented in both experimental and clinical reports that the pulmonic valve may be expendable, suggesting its use as a potential replacement for one of the indispensable valves. Earlier studies[1, 2] have indicated that it is technically feasible to remove the dog's pulmonic valve intact, and that, when transplanted to the descending thoracic aorta, the graft remains viable. The present investigation was undertaken to evaluate this pulmonic valve graft as a substitute for the mitral valve.

METHOD

In 26 preliminary experiments the pulmonic valve was excised, transplanted into the left atrium and fixed just above the mitral ring. In some of these animals the mitral valve was made insufficient by incising the leaflets or the chordae tendineae. These experiments will not be described in detail, but they provided experience for development of the present operative technique. Certain encouraging observations were made. Twelve of these dogs were studied for periods ranging from 10 days to one year. Frequently, death occurred from bacterial endocarditis which indicated the need for careful aseptic technique. Five of the animals, sacrificed from 3 months to one year after operation, demonstrated that the transplanted valve had survived in its new intracardiac position and appeared capable of normal function (Fig. 1).

In 22 subsequent experiments, with which this report is primarily concerned, the graft was put to a more critical test by completely removing the mitral valve prior to insertion of the autologous pulmonary valve graft.

Mongrel dogs, weighing 17 to 28 kilograms, were used. The animals were anesthetized with intravenous pentobarbital, 30 mg. per kilogram, intubated, and ventilated with 100 per cent oxygen except during the period of cardiopulmonary bypass. This operative procedure was carried out in each case under aseptic conditions comparable to those employed in the operating room.

The heart and great vessels were exposed through a left thoracotomy incision in the fourth or fifth intercostal space. After division of the anterior mediastinal reflections

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and ligation of the azygos vein, the venae cavae were looped with umbilical tape. The pericardium was incised anterior to the phrenic nerve and the edges sutured to the wound margins. After intravenous administration of heparin, 2 mg. per kilogram, catheters were inserted through the external jugular and femoral veins, and a cannula was placed in the femoral artery. A small catheter was also inserted for left atrial drainage. A rotating disc oxygenator was used for cardiac bypass and a flow of 70 to 90 c.c. per kilogram per minute was selected. The pulmonary artery and aorta were clamped through the transverse sinus, and, during the period of cardiac anoxia, the surface of the heart was lavaged with saline at 4° C.[3] Blood for priming the oxygenator was cooled so that the rectal temperature fell to 29° to 31° C. during perfusion.

The pulmonic valve and annulus were first removed by employing the technique described in a previous report.[1] Continuity between the right ventricle and pulmonary artery was re-established with a short segment of fresh homologous aorta. In later experiments a segment of Teflon tube was found to be preferable. During this first stage of the procedure, which required approximately 30 minutes of cardiac anoxia, the heart displayed a barely perceptible ventricular fibrillation.

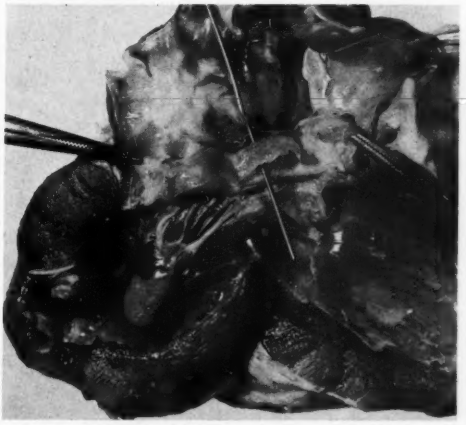

Fig. 1.—The autologous pulmonic valve graft sutured to the mitral ring. Chordae tendineae to the aortic leaflet were severed to produce insufficiency. The dog was sacrificed 6 months after operation and the graft was found in good condition except for a small hole in the base of one cusp.

Excellent exposure of the mitral valve was obtained through an incision in the atrial appendage with retraction of the edges. The valve leaflets and chordae tendineae were excised completely, leaving only the mitral annulus. The pulmonic valve graft was then turned inside out and placed within the left ventricle. The pulmonary artery edge of the graft was fixed with a continuous silk suture to the mitral annulus. The graft was again inverted with a "pull-through" maneuver bringing the myocardial border back into the atrium. This muscular edge was fixed to the atrial wall by interrupted silk sutures carefully placed in order to avoid occlusion of the pulmonary veins. The atriotomy was closed with a running suture.

Removal of the mitral valve and fixation of the pulmonic valve graft may be carried out after release of the aortic clamp, and the heart will almost invariably continue to fibrillate. However, in most of these experiments the aorta and pulmonary artery remained clamped and myocardial cooling was continued throughout the entire transplantation procedure. This provided a quieter heart and the additional 20 to 30 minutes of cardiac anoxia was well tolerated. With either technique, bronchial drainage from the pulmonary veins was removed by a suction tip in the left atrium.

Following disocclusion of the aorta and a brief period of coronary perfusion, the heart was defibrillated electrically and bypass was gradually discontinued. After removal of the catheters and administration of Polybrene, the wound was closed in layers.

RESULTS

Six animals died during operation or in the first 24 hours due to technical errors. In 2 of these the right coronary artery was inadvertently occluded, and ventricular fibrillation occurred soon after bypass was discontinued. Three animals died several hours after operation of severe "mitral" insufficiency due to damaged valve cusps by misplaced sutures in the graft. The high left atrial pressure was clearly visible prior to closure of the chest. One dog died 18 hours after operation of hemothorax and atelectasis.

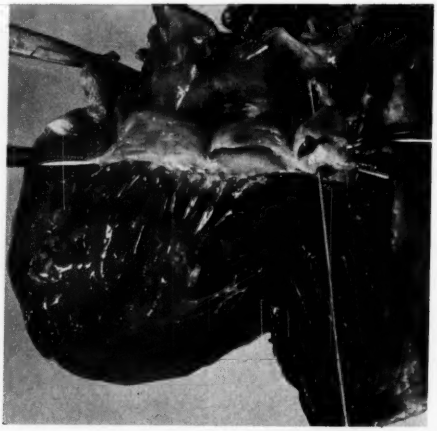

Fig. 2.—A pulmonic valve graft 10 weeks after operation. A portion of the distal suture line has disrupted and there is left ventricular dilatation.

Seven animals died or were sacrificed between one and 10 weeks after operation; all had developed cardiac decompensation. In each case the autopsy specimen (Fig. 2) showed partial disruption of the suture line with resulting insufficiency of the valve graft. The need was well demonstrated for deep sutures in the mitral annulus, especially laterally where it is a less well-defined structure.

One dog was sacrificed at 7 weeks when it developed signs of severe right heart failure. At autopsy the segment of homologous aorta connecting the right ventricle and pulmonary artery was almost completely occluded by an organized thrombus which was firmly adherent to the intima. The autologous valve graft appeared to be in excellent condition with the suture lines intact and no evidence of valvular insufficiency.

Two animals died at 7½ and 9 months, also as a result of complications from the segment of homologous aorta. Both dogs developed right heart failure due to marked sclerosis and contracture of the homograft. One demonstrated some thickening and deformity of a valve cusp which may have

been damaged in transplantation of the graft. In the second animal the transplanted valve proved to be in excellent condition, firmly fixed to the mitral annulus and the atrial wall (Fig. 3). The valve cusps were thin and pliable, and competence was demonstrated by squeezing the left ventricle when filled with water. With the aorta occluded, the cusps were observed to bulge into the atrium without regurgitation of water.

One animal appeared healthy and vigorous for 7 months after operation at which time a second thoracotomy was done to observe the heart chambers and to obtain a direct left atrial pressure tracing. The pressure curve revealed a sharp systolic peak which suggested valvular insufficiency. The left atrium and ventricle were not enlarged and there was no evidence of cardiac decompensation. A subsequent cineangiogram made after the injection of 50 per cent Hypaque into the left ventricle revealed the valve to be competent. A striking feature demonstrated by the film was the systolic bulging

Fig. 3.—A pulmonic valve graft 9 months after transplantation. The suture lines are well healed. The cusps remain thin and pliable and there is no evidence of thrombus formation. Cotton has been placed beneath the cusps for the illustration.

of the pulmonic semilunar cusps into the atrium without regurgitation of the contrast material. Apparently this bulging of the cusps accounted for the abnormal atrial pressure curve. This animal died one month later of empyema and lung abscess, apparently a complication of the second thoracotomy. The transplanted valve was in excellent condition (Fig. 4). The cusps were thin and pliable, and there was no evidence of valvular stenosis or insufficiency. The valve ring circumference measured 7 cm. The segment of Teflon tube between the right ventricle and pulmonary artery was well lined with endothelium and showed no evidence of stenosis or thrombosis (Fig. 5). Microscopic studies of the transplanted valves demonstrated that the myocardial tissue became replaced by fibrous tissue and collagen. The pulmonary artery and cusp tissue remained unchanged and small blood vessels were seen in the deeper portions of the graft, resembling vasa vasorum.

Five animals remain in good health one year postoperatively, and the valve grafts appear to be functioning well. Two have had cineangiography performed (Fig. 6). One demonstrated a competent valve and the other showed a small regurgitant jet in the inferior portion of the valve ring, possibly due to a misplaced suture. The remaining 3 have undergone secondary thoracotomy with inspection of the heart and a left atrial pressure

Fig. 4.—A transplanted pulmonic valve 8 months after operation. This animal died of empyema following a secondary thoracotomy.

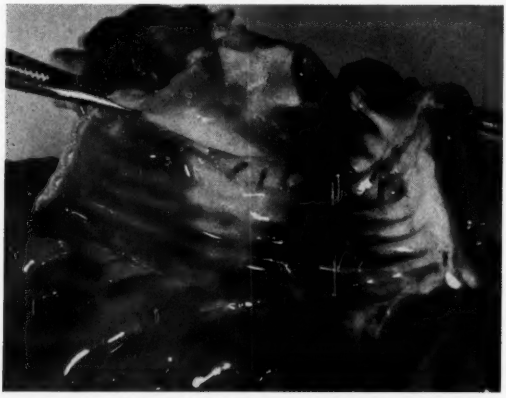

Fig. 5.—A short segment of Teflon tubing was found to be superior to the homologous aorta used in earlier experiments for joining right ventricle to pulmonary artery. This specimen was removed 8 months after operation and is from the same animal as that shown in Fig. 4.

obtained with a catheter threaded through a small pulmonary vein. These animals appear to have competent valves with the exception of one which demonstrated a definite regurgitant wave on the tracing. Despite the obvious presence of some "mitral" regurgitation, this dog remains vigorous and active without evidence of cardiac decompensation. One animal delivered a litter of pups without difficulty 8 months after operation.

DISCUSSION

This paper must be considered in the nature of a progress report since these animals with mitral valve replacement have been observed for only one year. The evidence, however, suggests that this type of autologous graft is at present superior to what can be accomplished with synthetic materials. There has been no problem with thrombosis or deterioration of the graft and permanent fixation should be technically much easier than it is with a plastic prosthesis.

Fig. 6.—Cineangiography was performed with injection of 50 per cent Hypaque into the left ventricle through a loop catheter passed retrograde from the carotid artery. The semilunar cusps of the valve graft are indicated by the arrows.

The best method for restoring continuity between the right ventricle and pulmonary artery is unsettled. Homologous aorta which was used to facilitate the operative procedure was found unsatisfactory because of the tendency for stenosis or thrombosis to occur. A short segment of Teflon tube was found to be satisfactory, but this technique has been incompletely evaluated. Autopsy studies on human hearts demonstrated that the pulmonary artery can probably be sutured directly to the cut edge of the right ventricular outflow tract after removal of the pulmonic valve.

The important question which remains unanswered is the possible clinical application of pulmonic valve transplantation in view of the pulmonary hypertension which is associated with mitral valve disease. There is some evidence which indicates that this form of pulmonary hypertension is not "fixed" and rapidly subsides when the mitral lesion is adequately corrected. An experimental preparation in which the mitral lesion and pulmonary hypertension are induced prior to the valve transplantation would more nearly simulate the clinical problem and provide useful information. The current study, however, is encouraging in that the transplanted valve seems to substitute quite adequately for the resected mitral valve, and the dogs remain vigorous, despite free pulmonic regurgitation.

SUMMARY

A technique has been presented for removal of the mitral valve in the dog and replacement with the autologous pulmonic valve. Autopsy specimens studied up to 9 months after operation show that the transplanted valve remains viable, and thrombosis or necrosis of the graft has not occurred. Five animals remain in good health one year after operation.

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DISCUSSION

(PAPERS BY MAGOVERN [PAGE 642], LOPEZ-BELIO [PAGE 648], ABBOTT [PAGE 660], STARR [PAGE 673], DOUMANIAN [PAGE 683], AND LOWER [PAGE 696] AND THEIR ASSOCIATES)

DR. CLARENCE CRAFOORD, Stockholm, Sweden.—I want to comment on Paper No. 25, an excellent presentation by Dr. Abbott of this anomaly. These cases are rare and since our first case in which we performed operation 15 years ago, we have only encountered one more about 6 months ago.

[Slide] You see here an angiocardiogram of this patient which demonstrates the filling of the coronaries with a wide tortuous coronary entering directly into the pulmonary artery. This patient was also operated upon with double ligation and division of the abnormal coronary artery entering the pulmonary artery.

DR. ARTHUR M. VINEBERG, Montreal, Quebec.—I am delighted that there is still someone interested in the problem of the surgical treatment of myocardial ischemia.

After reading the program of this meeting one cannot help but be impressed by the overwhelming attention that is being directed toward the surgical treatment of acquired valvular and congenital heart lesions, in spite of the fact that one of every four deaths in North America is caused by coronary artery insufficiency.

Dr. Julian's approach to the implantation of a systemic artery, such as the internal mammary artery, into the myocardium is an interesting one and, I am sure, in certain cases, may be of value. He pointed out that a high percentage of implanted internal mammary arteries in his cases remained open as compared with a much smaller number of "Vineberg implants." In describing the technique he used for performing a "Vineberg implant" Dr. Julian related how the internal mammary artery was implanted into the myocardium with all of its branches closed. I am surprised that 40 per cent of such implants remained open. The technique which has been described was reported by us before this meeting in Quebec in 1945 and was published in the JOURNAL OF THORACIC SURGERY in December, 1949.

In that publication we described the placing of an internal mammary artery into the ventricular myocardium with all of its branches and end closed and reported that 96 per cent of these implanted arteries in 88 animals thrombosed. It was after this experience that it was realized that in the heart, as elsewhere, an artery blocks back to the first open branch. All the implants after that time were made with the sixth intercostal and other intercostal arteries open and bleeding into the myocardial tunnel. This technique has been described frequently and, in the ischemic animal heart, we have found that over 80 per cent of implants performed in this way remained open in the ischemic heart. [Slide] This shows an internal mammary artery which has been implanted for over a year. The left heart has

been made ischemic by Ameroid coronary constrictors. The only injection was made through the origin of the internal mammary artery with Schlesinger mass and the roentgenogram shows how the entire left heart and part of the right has been filled by this injection.

The following moving picture has been taken from a cineangiocardiogram of a living animal 12 months after implantation, and shows quite clearly the direction of flow down the internal mammary artery, into the heart, where the proximal positions of the coronary arteries can be seen to fill.

Similar results have been obtained by many other workers. Recently, McLean, following our technique of implantation of the internal mammary artery, has found at least 80 per cent of the implanted arteries open when left in an ischemic animal heart. He also found that such implanted internal mammary arteries prevented a decrease in the threshold of ventricular fibrillation after ligation of an anterior descending branch of the left coronary artery.

McMillan, of the Royal Victoria Hospital, has studied 15 human hearts from patients who had undergone internal mammary artery implantation and had died from one reason or another up to 4 years after implantation. Ten of the fifteen arteries examined were open, four were patent between 1½ to 4 years after implantation. In the human arteries examined, the patency ranged from 70 to 95 per cent. Internal proliferation, although present, was not extensive in the majority of implanted vessels. In one case the only artery open in the heart was the implant placed there 4 years previously.

In another case, 22 months after internal mammary artery implantation, there was no clinical improvement. The patient was returned to the operating room where a pulsating internal mammary artery was identified and the Ivalon sponge operation was performed. The patient improved, returned to work, and died in a fight 20 months after his sponge operation and 3½ years after internal mammary implant.

[Slide] This drawing has been made to scale to demonstrate the degree of patency of this patient's coronary arteries and his implanted internal coronary artery at the time of his death. It should be noted that there was complete occlusion of the right coronary artery, 95 per cent of the circumflex artery, with an 80 per cent occlusion of the anterior descending coronary artery. The implanted internal coronary artery was 70 per cent patent. It is clear that this artery alone could not supply sufficient blood to replace the patient's blocked or narrowed major coronary arteries which had an average cross-sectional area open. In spite of this extra load which the internal mammary artery had to carry, it remained 70 per cent patent for 3½ years while lying within an ischemic human left ventricular myocardium.

At present we are experimenting with Teflon grafts attached to the aorta at one end and buried in the myocardium, introduced into the left ventricular lumen.

DR. HENRY SWAN, II, Denver, Colo.—I should like to lend some dignity to Dr. Magovern's technique by commenting on the history of the use of splints in arterial anastomosis. [Slide] You all recall that Dr. Payr described a splint in 1900.

[Slide] Dr. Crile also used this technique but added the refinement of having a clamp which would hold the prosthesis.

In the period of direct transfusion, arteriovenous anastomosis between the donor and recipient was the common technique and Dr. Soresi in 1911 developed this clamp [slide] for the purpose—you see he has the little hooks on this clamp and the clamp takes the ends of both the artery and the vein and pulls them together mechanically, which in 1911 was a rather advanced instrument.

Finally, Dr. Landon, of Philadelphia, developed the instrument [slide] which has all of the features of the Donetski ring; a ring structure with host-to-host vessel and a forceps technique to hold the entire gadget with the inversion of the end into the opposite end to be anastomosed.

[Slide] This next slide shows the Russian modification, currently called the Donetski ring, which is a ring with hooks on it, and the method of application of that technique.

DR. ROSS ROBERTSON, Vancouver, British Columbia.—I was particularly interested in Dr. Julian's paper in which he discussed the Vineberg operation. [Slide] In spite of performing the Vineberg operation as described, leaving the ends of the artery and a few branches open within the myocardium, after a few weeks or months, when the animal was destroyed, the artery was found to be almost completely occluded by intimal thickening, as shown in this slide.

[Slide] Consequently we tried the technique of implanting the artery in continuity by dissecting it free up to the subclavian artery, making an incision in the myocardium and implanting the loop of artery intact so that the circulation was continuous. In these animals the implanted internal mammary artery remained open, as shown in the angiogram [slide]. The two metal clips indicate where it is implanted in the myocardium. Unfortunately, no gross collaterals developed.

[Slide] This slide made from a postmortem section several months after operation shows the artery implanted in continuity to be widely patent. It is my opinion that further work along these lines should be continued.

DR. EGBERT H. FELL, Chicago, Ill.—We have encountered, to date, six coronary artery-right ventricular fistulas. Five have been of the congenital type, one the iatrogenic. Four of the six have been diagnosed preoperatively by the Pediatric Cardiologists at the Cook County and Presbyterian-St. Luke's Hospitals. Three of the congenital cases were of right coronary arteries entering directly into the right ventricle; 2 ran from the left coronary artery into the right ventricle. We agree with Dr. Abbott in reference to saving the coronary artery if possible.

[Slide] The patients ranged from 14 months to 18 years of age. This slide shows a venous angiocardiogram in a 14-month-old boy, and you see the large right coronary going into a fistulous aneurysmal dilatation at the apex of the right ventricle.

[Slide] Postoperatively, the angiocardiogram shows that the coronary is well visualized but the fistulous tract and the aneurysm are not present.

[Slide] This retrograde aortogram shows a large aneurysmal dilatation of the right coronary artery to 6 cm. in diameter. When such a problem as this is encountered the fistula is closed and the aneurysm resected; in 2 patients it was necessary to close off the coronary artery near its origin, because the huge artery was doing more harm than good.

To conclude, the diagnosis of these rare anomalies has been made preoperatively in 4 of 6 patients. The presence of a machinery murmur in an unusual location should prompt an angiocardiogram or retrograde aortogram. The 6 patients have been operated upon and their lesions successfully repaired; there are no residual murmurs or abnormal electrocardiograms.

DR. DENTON A. COOLEY, Houston, Texas.—Apropos of what Dr. Abbott has stated regarding the importance of preserving the parent coronary artery in these patients, our experience should be of some interest. [Slide] We have had 5 patients with coronary arteriovenous fistula who have come to operation; there was one death. The death occurred in an acutely ill 5-month-old patient in whom the fistula was not recognized at thoracotomy, since a left thoracotomy was used because of a mistaken diagnosis. The anomaly involved the right coronary artery and was not visible from this approach. In fact all of our surgical cases proved to be right coronary to right ventricular fistulas.

In 3 patients, aged 4, 11, and 13 years, respectively, uncomplicated and complete recovery followed suture ligation of the coronary fistula with proximal and distal ligation of the right coronary arteries. In a 40-year-old woman the same method for closure of the fistula was used after a 15-minute period of temporary coronary occlusion showed no significant changes in the electrocardiogram. In this patient, proximal and distal ligation with obliterative aneurysmorrhaphy was used and she did well for several hours. Fortunately, she was connected to a continuous monitor of the electrocardiogram because she suddenly developed cardiac standstill followed by ventricular fibrillation. Because of the alertness of Dr. Paul Ellis, a cardiac massage and electrical defibrillation was successful, and she finally made a complete recovery.

On the basis of this small series of 4 successful cases of coronary ligation one might assume that ligation of the right coronary artery in children may be well tolerated, whereas in adults this may lead to serious consequences.

DR. FREDERICK H. TAYLOR, Charlotte, N. C.—I should like to emphasize two points: (1) the diagnosis of this anomaly can be made preoperatively, and (2) the fistulas should be surgically corrected.

The clinical picture of coronary A-V fistula is that of a systemic A-V fistula with an intracardiac shunt. [Slide] This heart shows evidence of a left-to-right shunt—that is, an increased pulmonary vascular margin and dilatation of the right ventricle. In addition, there may be a widened pulse pressure, enlargement of the left ventricle, and deviation of the electrical axis to the left. There is also a systolic-diastolic murmur. We feel that this unusual combination of findings seems typical for a coronary A-V fistula.

[Slide] This is a phonocardiogram showing the systolic-diastolic component of the murmur.

[Slide] Cardiac catheterization is important in diagnosis by showing increased oxygenation in the coronary sinus or in one of the right heart chambers. Here we see an increase in oxygenation in the lower atrium [slide], which was due to an A-V fistula. The clamp is pointing out the large afferent limb emptying into the coronary sinus.

[Slide] In this slide we see an increased oxygenation in the right ventricle which is due to the emptying of the coronary fistula into the right ventricle.

[Slide] This slide shows post-ligation of this fistula.

Our main emphasis is that these fistulas should be surgically corrected to improve the myocardial capillary blood flow and to lessen the heart work.

DR. WARREN J. TAYLOR, Boston, Mass.—I rise to report to this Association a follow-up on the caged ball valve used as a prosthetic replacement for the aortic valve. You may recall last year at the Annual Meeting of this Association that Dr. Dwight Harken outlined an initial series of 5 patients, with one survivor. He pointed out in some detail the reasons for the failures. This material has since been published in the JOURNAL of this Association in greater detail. In that initial series there were 2 additional patients, one of whom survived.

At that point in our experience we stopped doing this procedure and observed these 2 survivors for a full year. During this period they continued to do extremely well. They did not destroy the formed elements in the blood, there was no anemia, and they did not show evidence of embolization.

We have recently started a second series. Five additional patients have been operated upon, with 3 survivors. Both patients who failed to survive were "re-operation patients." One had previously been operated upon by closed technique; the other by open technique with plastic reconstruction of the aortic valve. Both patients were troublesome in terms of vascular adhesions and bleeding. The death of one patient was directly attributable to this complication. The second patient had extremely thin valve leaflets. This tissue defect was the basis of the recurrent aortic insufficiency. The original plastic repair was intact. Fixation and proper seating of the caged ball valve was difficult. (This technical problem has since been corrected.) During the first 4 postoperative days this patient's course was excellent, with normal hemodynamics present; thereafter, free regurgitation developed with a fatal result.

We are impressed with the stability of this type of prosthesis and greatly encouraged by the long-term results in the 2 original patients who have now been followed for over one year.

DR. MAGOVERN (Closing).—This method, as Dr. Swan pointed out, is not new but it previously fell into disrepute primarily because it was attempted in many cases of trauma and thrombosis subsequently occurred, more on the basis of the injury than on the actual technique.

DR. JULIAN (Closing).—We characterized the procedure of implantation of the mammary artery into the myocardium as a modification of the Vineberg operation in recognition of the fact that this had been described so ably and has so long been worked on by Dr. Vineberg. I was careful to point out in my presentation that this manner of implantation with the branches of the end of the vessel ligated is a deviation. Some of these implants remained open.

It was found necessary to ligate the branches because, in implanting a continuous flow loop of the type we have described today, the presence of open branches produces a hematoma which frequently destroys the preparation.

We avoided the use of Ameroid cuffs in the partial occlusion of the coronary artery preparation by using cotton ligatures, partially tied. In 88 per cent of the animals this goes on to complete occlusion, just as does an Ameroid cuff, and avoids the presence of a rather large structure.

Finally, I would like to stress the fact that we don't have enough confidence in the implantation of the artery for a continuous flow loop to use it clinically or to recommend its use.

Dr. Robertson's method of implanting a continuous flow mammary loop is, of course, a similar preparation, the same in all fundamentals. The endothelial proliferation that he so clearly demonstrated in his slide was a major difference between our continuous flow loop and our simple implantation of the artery. The latter shows a good deal of endothelial proliferation, but when continuous flow is obligatory, it did not appear.

The lack of mammary-coronary communication in Dr. Robertson's preparation would parallel the lack of communication in our own work in the absence of a previously induced myocardial ischemia.

DR. ABBOTT (Closing).—I wish to express my pleasure in hearing of Dr. Crafoord's original and continued experience with this anomaly. The lateral view angiogram which he showed illustrates a point which Dr. Fell and others have stressed, namely, that biplane visualization is often essential for diagnosis. An anteroposterior roentgenogram, alone, can easily be misinterpreted as representing a ruptured sinus of Valsalva. Biplane angiocardiography or cineangiography is needed to differentiate these two lesions.

I wonder if Dr. Beck and others would agree with Dr. Cooley about the lesser need of preserving individual coronary arteries in children who have had neither time nor the impetus to develop useful intercoronary collaterals. At least on theoretical grounds I suspect that we have a greater fear of sacrificing a coronary vessel in children than in the adult.

The increased heart work in the presence of this lesion, commented upon by Dr. Taylor, has been shown by catheter studies to vary greatly in individual cases. In our second case, the shunt is extraordinarily small. We do not feel justified in doing anything in this case so long as the cardiogram is normal, the heart size remains normal, and catheter data indicate a minimal shunt.

The cardiac catheterization studies reported in the literature have not uncommonly shown the shunt to be less than one would suspect.

DR. STARR (Closing).—I would like to make one additional point concerning the clinical use of the mitral ball valve prosthesis. The prosthesis can be inserted quite easily and rapidly, taking about 20 to 25 minutes at most. The surgeon, therefore, has considerable time during open operations on the mitral valve to do anything that he thinks may be proper to restore the valve to normal function. Bypass may be discontinued and left atrial pressure measured. If he is dissatisfied with the results he has the means better to insure the patient's survival by using the prosthesis at the same operation.

Announcement

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Forty-second Annual Meeting of The American Association for Thoracic Surgery will be held April 16, 17, and 18, 1962, in St Louis, Missouri. Headquarters will be The Chase-Park Plaza Hotels.

Requests for Hotel Reservations

These should be mailed directly to Mr. T. J. Robinson, Executive Assistant Manager, The Chase-Park Plaza Hotels, St. Louis 8, Missouri. Please mention this Association, the type of accommodation desired, the date, and approximate hour of arrival and departure. If accommodations are desired elsewhere please communicate directly with the hotel of your choice.

Material for the Program

SCIENTIFIC PAPERS.—Abstracts of all papers proposed for presentation at the 1962 meeting *must be received on or before* **November 15, 1961,** otherwise they will not be considered by the Program Committee. These should contain *not more than* **200** *words* that accurately and clearly reflect the content of the completed paper. They should be labeled "For Thoracic Surgery Forum" or "For Regular Program," depending upon the nature of the subject matter. The Forum is primarily for the presentation of short papers on current thoracic research, experimental problems, anatomical studies, and modified or new surgical techniques.

Six, repeat, six clearly legible copies of each abstract must be sent to Miss Ada Hanvey, Administrative Assistant, The American Association for Thoracic Surgery, Suite 311 Carondelet West, 7730 Carondelet Avenue, St. Louis 5, Missouri.

Essayists selected for the program are reminded that papers presented at the meeting are to be published in the Journal and *must* be handed to the secretary *immediately* after their presentation. The maximum length allowed for Forum papers is 3,000 words without illustration. If illustrated, an appropriate number of words must be subtracted.

Applications for Membership

Applications for Associate Membership in the Association must be received by the Membership Committee *not later than* **November 15, 1961,** otherwise the application will be deferred for consideration until the 1963 meeting.

Applicants must be sponsored by three Active or Senior Members of the Association. In addition to the signature on the application form, the sponsors will forward a *separate* letter concerning the applicant directly to:

Charles K. Kirby, M.D.
Chairman of the Membership Committee
3400 Spruce Street
Philadelphia 4, Pennsylvania

Sponsors are reminded that *new* letters of recommendation must be forwarded to the Chairman of the Membership Committee should their applications be held over for reconsideration a *second year.*